# The Journal

OF THE KANSAS MEDICAL SOCIETY

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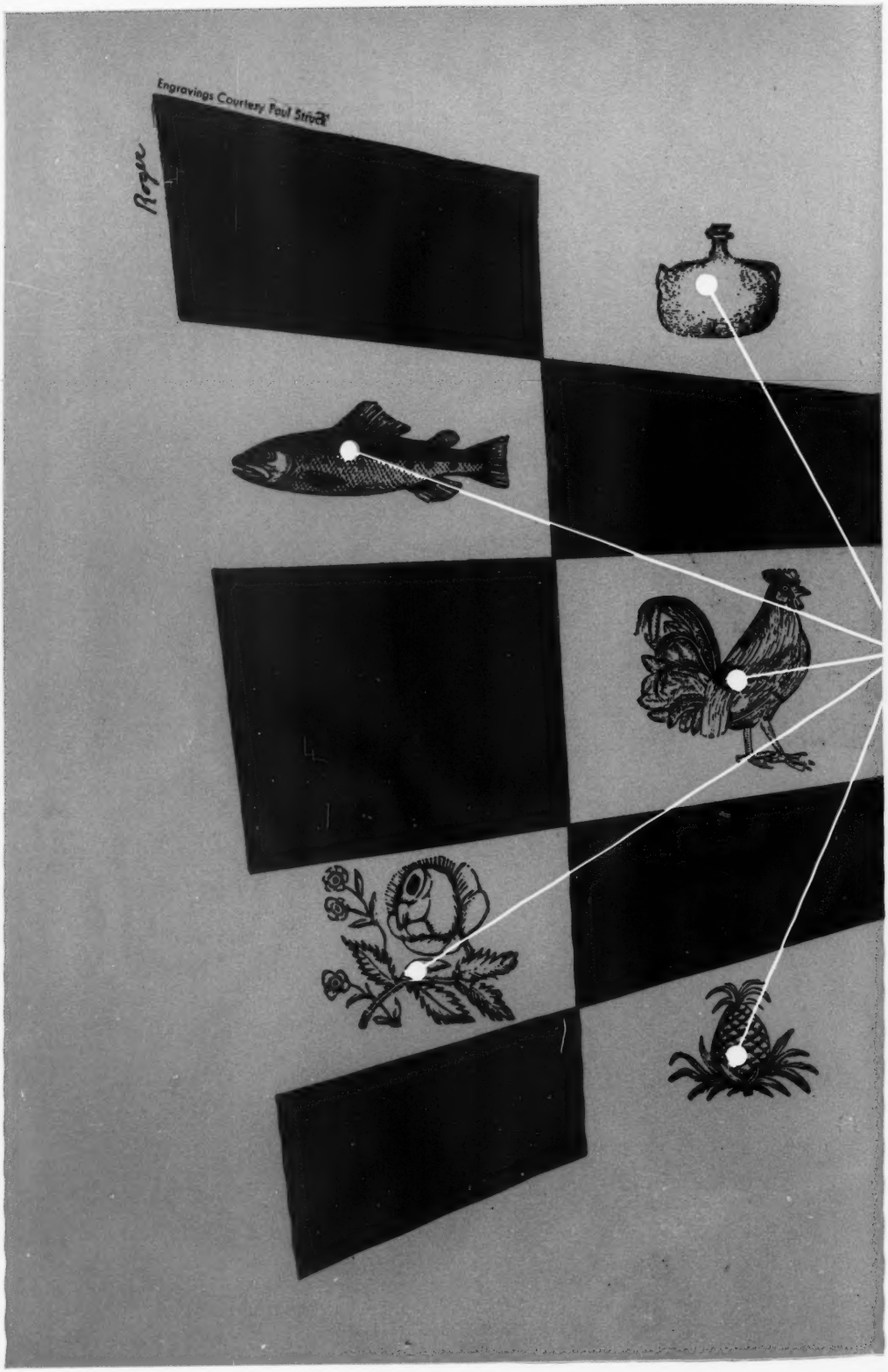
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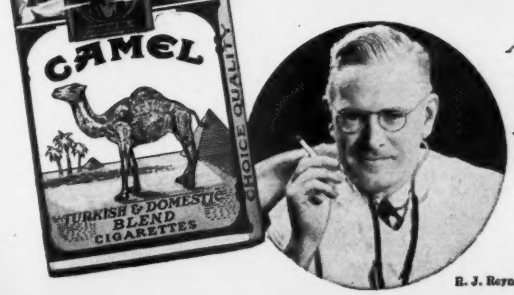


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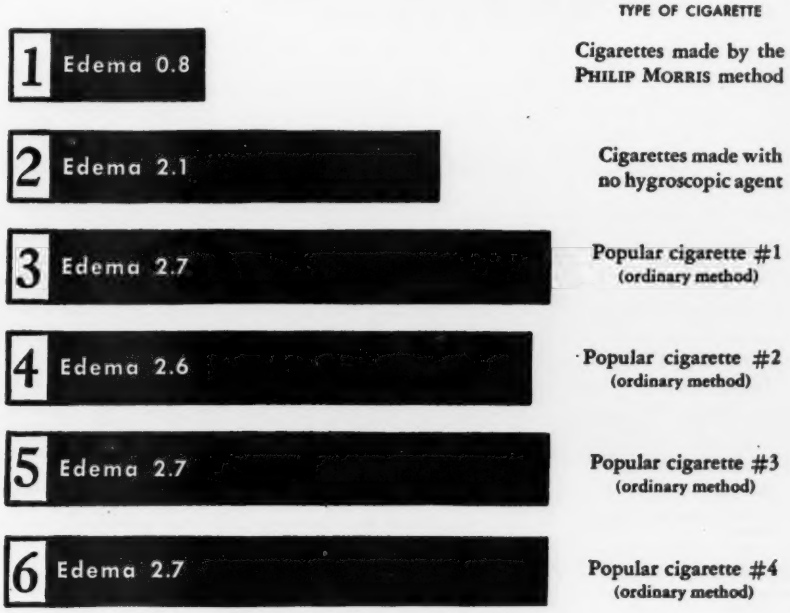
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**N. Y. State Journ. Med. 35 No. 11,590* ***Laryngoscope 1935, XLV, No. 2, 149-154*

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# STREPTOMYCIN*

Wallace E. Herrell, M.D.**

Rochester, Minnesota

Before I consider the new antibiotic, streptomycin, it is well to reflect a moment on what has happened in the last few years in the treatment of bacterial infections. Until approximately ten years ago the antibacterial agents for clinical use were, to say the least, feeble. The last ten years have seen the development of, first, the sulfonamides, followed by tyrothricin (gramicidin), then penicillin and, more recently, streptomycin. The development of penicillin was greatly accelerated by the stimulus of the recent war. Unfortunately, Fleming's observation, which was made in 1929, did not receive its deserved attention until the Oxford investigators isolated penicillin in a form suitable for clinical use in 1940. I think it can be stated fairly that experience in the development of the other antibiotic, penicillin, greatly fostered advances in the development of streptomycin.

An antibiotic is an agent which is elaborated by a microbe and which can be isolated and used in the treatment of infections commonly encountered in man. In other words, antibiotic agents are of microbial origin. There are, in general, three sources of antibiotic agents. One source is bacteria; another, molds and fungi and the third is actinomycetes. Perhaps the most important antibiotic agent derived from bacteria is tyrothricin and the most important to date derived from molds and fungi is, of course, penicillin. Streptomycin is an example of an antibiotic derived from actinomycetes. The whole concept of use of antibiotic agents in treatment is based on the theory of bacterial antagonism. This is, by no means, a new theory. It has been known since the days of Pasteur. Unfortunately, most of the antibiotics known during the early days of bacteriology were too toxic for systemic use.

Streptomycin was described first by Schatz, Bugie and Waksman in January, 1944. The substance was obtained from Streptomyces griseus; hence its name "streptomycin." The great interest in streptomycin lies in the fact that it is effective against certain important gram-negative organisms, many of which are not inhibited by penicillin. Furthermore, streptomycin appears to exert an antibacterial effect on Mycobacterium tuberculosis. At the Mayo Clinic studies on streptomycin began in the spring of 1944. Feldman and Hinshaw later reported on the possible effect of streptomycin in experimental and clinical tuberculosis. My interest in streptomycin has been in its use in the treatment of infections other than tuberculosis, particularly those due to sensitive gram-negative organisms.

It was evident from the early reports on streptomycin that this agent should prove effective in the treatment of infections due to Klebsiella pneumoniae (Friedlander's pneumonia) and such infections as ozena and rhinoscleroma in which this organism commonly can be isolated. In experimental studies streptomycin was found to be effective in the treatment of tularemia and subsequent clinical studies confirmed this impression. Streptomycin also has an inhibitory effect on certain other important gram-negative organisms, such as those belonging to the colon-typhoid-dysentery group. It inhibits the growth of certain important organisms commonly found in the urinary tract, such as Proteus ammoniae and Aerobacter acrogenes.

At this point I would like to mention something about the bacteriologic facilities needed in the hospitals where patients receive modern-day chemotherapy for bacterial infections. Now that selective antibacterial agents are available, better and more adequate bacteriologic study of patients is important. This need poses a real problem to those interested in hospital administration. I am sure that most physicians can remember the time when the type of organism causing an infection was not particularly important because the treatment was largely empirical and, to say the least, not very satisfactory.

*Read at the annual meeting of the Kansas Medical Society, Wichita, Kansas, April 24, 1946.

**Division of Medicine, Mayo Clinic.

Today good chemotherapy requires close collaboration between the bacteriologist and the clinician.

Physicians have now learned something about what happens to streptomycin once it is administered to the patient. In general, it behaves not unlike penicillin following its administration by the intramuscular, subcutaneous or intravenous route. Streptomycin diffuses fairly readily throughout most body tissues. Levels in the blood are usually highest about two or three hours after the injection. By repeated injections the level of streptomycin in the blood can be built up rather high. In this respect it differs somewhat from penicillin. Streptomycin appears to be excreted rather readily by the kidneys. Approximately 60 to 80 per cent of the amount given will be excreted in the urine within twenty-four hours after administration. Streptomycin finds its way into the cerebrospinal fluid but appears to diffuse into this fluid more readily in the presence of inflammation. It does not appear to reach the brain tissue in significant concentrations. Streptomycin is excreted in bile and, therefore, should prove of value in the treatment of certain infections in the biliary tract. Streptomycin diffuses through the placenta and, therefore, if it is present in the maternal circulation, it is also present in the fetal circulation. In this respect it behaves much like penicillin. Small amounts of streptomycin also are excreted in breast milk. This means that the nursing infant may receive it by mouth. This fact should cause no great concern because its oral ingestion is not followed by its appearance in the circulation of the infant nor, for that matter, in the adult. The only possible result following oral ingestion is a reduction in certain bacteria in the intestinal flora. The failure of streptomycin to reach the general circulation following oral administration of even enormous amounts is of some importance. In this respect it differs from penicillin, for some penicillin will reach the general circulation after oral administration. As far as streptomycin is concerned, I think this attribute is perhaps fortunate because patients cannot obtain the material and treat themselves by oral administration. As I have already pointed out, the only result that can follow oral administration of streptomycin is a reduction in the sensitive bacteria present in the intestinal tract. This immediately suggests one possible future use of streptomycin; namely, its use in the preoperative preparation of patients for operations on the intestinal tract.

Streptomycin, unlike penicillin, is a fairly stable substance. Even in solution it can be kept a reasonable length of time without loss of potency. In early studies on streptomycin, the unit value was used. Recently quantities have been expressed in grams. One gram of streptomycin, as I shall use it henceforth in this paper, is equivalent to approximately 1,000,000 S units. In ordinary practice, the solution used for intramuscular administration usually consists of 1 gm. of streptomycin per 5 c.c. of distilled water. The average dose for adults is approximately 2 gm. and, in some instances, 3 or 4 gm. per twenty-four hours. The average daily dose for children is 1 gm.; however, on occasions as much as 4 gm. per day have been administered. In general practice, it is simply a matter of deciding on the amount to be used and then giving this amount in five to eight divided doses every twenty-four hours. This is usually given by either the subcutaneous or the intramuscular route.

Streptomycin also may be given by nebulization. For this purpose the solution should contain 50 mg. (50,000 units) per cubic centimeter. This method of administration is commonly used in the preoperative preparation of patients who are undergoing lobectomy for pulmonary suppurative disease. Penicillin and streptomycin are frequently combined and given by nebulization for this purpose. This results in a reduction of both the gram-positive and gram-negative organisms in the tracheobronchial tree. Streptomycin may be, and should be given by the intrathecal route in the treatment of meningitis. When spinal fluid is withdrawn, it is customary to administer 10 c.c. of a solution containing 100 mg. of streptomycin. I have already mentioned that streptomycin may be given by mouth; 1 gm. may be administered every six hours and this usually will result in marked reduction in the number of sensitive bacteria in the bowel.

### CLINICAL RESULTS

Some of the most striking clinical results obtained to date with streptomycin have been those which followed its use in the treatment of tularemia. In this disease streptomycin has clearly established its value. In the past, patients who had tularemia were frequently ill for as long as twelve to sixteen weeks and many failed to survive. To date no failures have been reported in cases of tularemia treated with streptomycin. The average dose of streptomycin used has been 2 gm. per day for seven to ten days. The clinical improvement is dramatic and recovery has been uneventful in all forms of tularemia treated.

Bacteriemia and infections of the urinary tract due to Escherichia coli also have responded satisfactorily to streptomycin. There have been some failures in this group due to the fact that the organism was resistant or became resistant to streptomycin.

Rather satisfactory results have been obtained in cases of bacteriemia and infections of the urinary tract owing to Proteus ammoniae and Aerobacter aerogenes. Infections of the urinary tract should be treated intensively for a short period, that is, five

to seven days. Treatment should not be begun until foreign bodies and obstruction have been removed from the urinary tract. The presence of foreign bodies or obstruction favors the development of resistance to streptomycin.

The organism, Hemophilus influenzae, is sensitive to the action of streptomycin. It is not surprising, therefore, that satisfactory results have been obtained in the treatment of influenzal meningitis with streptomycin. It is generally agreed, however, that in the severe cases treatment with streptomycin should be combined with sulfonamide therapy and probably also combined with serum therapy. Likewise, Hemophilus pertussis is sensitive to the action of streptomycin but clinical results to date have not progressed sufficiently so that any definite statements can be made about its value in whooping cough. Clinical trials are under way.

I mentioned earlier that the organism, Klobsiella pneumoniae, was sensitive to streptomycin. Use of this antibiotic has been found of value in the treatment of Friedlander's pneumoniae and it also appears helpful in the treatment of ozena. Unfortunately, the incidence of recurrence and the incidence of the development of resistance on the part of the organism is rather prominent in this group of infections.

In spite of the fact that the organisms belonging to the typhoid or paratyphoid group are reasonably sensitive to streptomycin in the test tube, the clinical results of its use to date in the treatment of typhoid fever have not been encouraging.

Although streptomycin for the most part is effective against gram-negative organisms, a few strains of Staphylococous sureus, a gram-positive organism, also are sensitive to streptomycin. My colleagues and I have had occasion to see recoveries from staphylococcal bacteriemia when the organisms were resistant to penicillin but yielded to streptomycin.

Pasteurella postis, the organism which causes plague, also is sensitive to the action of streptomycin. Plague, of course, is not an important disease in America; however, it is encountered occasionally in certain parts of this country. From the studies on animals reported to date, it is reasonable to assume that streptomycin should prove of value in the treatment of plague.

Early reports of an experimental nature suggested that streptomycin might prove of value in the treatment of undulant fever. The organism responsible for undulant fever is moderately sensitive to this antibiotic. Unfortunately, streptomycin was hailed as a cure for this rather common infection and this is not the case. Experience to date would lead me to conclude that streptomycin may be of some value in the treatment of undulant fever in the early acute stage with or without positive blood cultures. I do not believe, however, that this beneficial effect is much greater than that which can be obtained by using three ten-day courses of treatment with one of the sulfonamides, such as sulfadiazine. It should be pointed out also that the results obtained in the early acute stages can be evaluated only with difficulty for many persons recover spontaneously and blood cultures become negative for the organisms even without treatment. In the treatment of so-called chronic undulant fever or brucellosis of months' or years' standing, I am convinced that streptomycin is of little or no value.

Streptomycin has been used in a variety of other miscellaneous infections but clinical experience to date is not great enough to justify any final statements. One of my colleagues, F. R. Heilman, found that certain spirochetes were sensitive to streptomycin. It was tried, therefore, in a few cases of early darkfield positive syphilis. The results were not convincing; however, the lesions while under treatment would become darkfield negative, but relapses occurred. In light of our present knowledge we were using doses considerably lower than we are using today. In any event, I am inclined to believe that we will do well to continue the evaluation of penicillin in this disease before use of streptomycin is considered in the treatment of this infection.

I mentioned earlier the work of my colleagues, Feldman and Hinshaw, in connection with the use of streptomycin in experimental as well as clinical tuberculosis. I am not qualified to speak with authority on the chemotherapy of tuberculosis. I will try to summarize the impressions I have gained from observing their studies as well as those carried out by other investigators. The evidence seemed clear from animal (guinea pig) studies that streptomycin exerted a definite suppressive effect on the course of this infection. This work naturally led to a widespread interest in its possible value in clinical tuberculosis. The effect of this substance in certain cases of pulmonary and extrapulmonary tuberculosis, including cases of cutaneous tuberculosis, renal tuberculosis and tuberculous meningitis, have been investigated. I believe that these investigators are of the opinion that streptomycin exerts a suppressive effect but has not been hailed as a cure. As the matter stands, it is an important addition to standard forms of treatment. Unjustified publicity can lead to only one result. Patients will clamor for this new form of treatment and if its value is overstressed, patients may refuse conventional forms of treatment including sanatorial care. It is the responsibility of the medical profession to see that this does not occur. I believe it is the general impression that if streptomycin is to be used in the treatment of tu-

berculosis, it must be used for a long period, perhaps months. In this group of cases certain neurotoxic reactions may occur. I will mention those later.

### TOXIC REACTIONS

After subcutaneous or intramuscular administration of streptomycin pain may occur at the site of injection. This is not a troublesome nor serious reaction. Certain toxic cutaneous reactions may follow its use, too. These reactions are not unlike those that follow the administration of penicillin to certain sensitive individuals. The reaction may take the form of a maculopapular rash or generalized urticaria. It use of the drug is discontinued, the cutaneous reaction will subside. On occasion my colleagues and I have been able to continue administration of streptomycin after a cutaneous reaction has occurred by changing from one batch of streptomycin to another. In this management of the cutaneous reactions benadryl (B-dimethylaminoethyl benzhydryl ether hydrochloride) or pyribenzamine (N'-pyridyl-N'-benzyl-N-dimethyl-ethylene diamine hydrochloride) is rather helpful. The usual dose of benadryl or pyribenzamine is 50 mg. three times per day. Individuals who are sensitive and who handle the solutions of streptomycin in the laboratory or elsewhere may develop a real dermatitis. In other words, an occupational dermatitis may be encountered.

Perhaps the most important toxic reaction encountered in connection with the use of streptomycin is the neurotoxic effect on the eighth nerve. This reaction imposes a real problem but it is not insurmountable. As a rule it is not encountered when streptomycin is used for a short period as for acute infections although on occasion I have seen it develop soon after treatment is started. It is encountered rather frequently, however, when streptomycin is used for long periods as is necessary in the treatment of tuberculosis. The reaction may take the form of vertigo which results from damage to the auditory branch of the eighth nerve. Both reactions may occur in the same patient. Experience shows, however, that the reaction of the eighth nerve usually will subside if administration of the streptomycin is discontinued soon after symptoms appear. This is a rather selective neurotoxic effect.

No other serious or significant toxic reactions have followed the use of streptomycin. There is no evidence to suggest that its use is followed by interference with normal renal function or that it has any toxic effect on the hematopoietic system.

### DEVELOPMENT OF RESISTANCE

I have mentioned before that certain organisms at times will develop resistance to streptomycin; in fact, some organisms will develop resistance to streptomycin with incredible rapidity. In the treatment of acute infections, therefore, intensive treatment for a short period of time is exceedingly important. Every effort should be made to reduce factors which favor resistance. Walled-off abscesses when present should be drained. Foreign bodies should be removed. Stasis and obstruction such as occur in infections of the urinary tract should be dealt with before treatment with streptomycin is begun. Finally, the pathogenic organisms should be tested for sensitivity before and during treatment. This testing necessitates frequent recourse to laboratory procedures which only the bacteriologist can furnish. As I said before, successful modern chemotherapy depends on close collaboration of the bacteriologist and the clinician. If an organism is resistant, or becomes resistant, to streptomycin, treatment will necessarily fail. The development of resistance on the part of the organism is far more important in connection with streptomycin therapy than experience at the clinic has shown it to be with penicillin. In fact, I do not subscribe to much of the current comment concerning the fact that penicillin is losing its powers. The development of resistance on the part of organisms to penicillin, although it does occur, has not been a major problem in penicillin therapy.

### COMMENT

To the investigator, all of these problems offer a great challenge. The past decade has been a great era in the treatment of important bacterial infections. Many problems remain unsolved but it is the hope of all investigators that in time agents effective in the treatment of most bacterial infections encountered in man will be developed.

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Spinal anesthesia requires as much skill and experience to administer properly as any other type of anesthesia. The care of the patient after the initial injection is just as important as during general anesthesia for the greatest safety and success of the method. Only the anesthesiologist has enough training and experience to use all the drugs and methods of this type of anesthesia. Others had best stick to one or two drugs that they have learned to use safely. Marked abnormalities in any of the three systems, respiration, circulation or central nervous system, usually make the use of this type of anesthesia inadvisable.

The length of the spine and the cerebrospinal fluid volume are more important in determining the dosage than the body weight. The rapid ascent of anesthesia level is more apt to produce a marked drop in blood pressure than producing the same level over a longer time. The circulatory depression is not caused by a specific drug but is related to the total area of the body anesthetized, plus the time over which this anesthesia is produced. In controlling the level of anesthesia, the gravitation factor is much more important than diffusion.—Ivan B. Taylor, M.D., in Jnl. of Mich. St. Med. Soc., November, 1946.

# PENICILLIN AND STREPTOMYCIN–A REVIEW OF THEIR CURRENT USES

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Antibiotics are substances prepared from the products of certain living organisms, particularly fungi. Some of these substances exert a powerful antagonist effect upon the life and growth of specific bacteria.[1] Emmerich and Loewe[2] in 1899 isolated a substance from *Pseudomonas aeruginosa* which inhibited the growth of diphtheria, cholera, plague and typhoid organisms. They called this substance pyocyanase. Pyocyanase was not of clinical value in as much as it poisons animal cells. In 1929 Fleming[3] observed that a mold which had contaminated his culture plates lysed straphylococcal colonies. His inquiring mind led him to the knowledge that this mold, later identified as Penicillin notatum, Westling, produced a substance which inhibited the growth of pyogenic cocci and the diphtheria-group of bacteria. The colityphoid and influenza bacilli were unaffected. Fleming gave to this antibacterial substance the name penicillin. In these early years following the discovery of penicillin few clinical trials were made and the substance was used by Fleming as a bacteriological tool.

In 1935 Domagk[4] reported that sulfamidochrysoidine, which is hydrolyzed in the body to sulfanilamide, protected mice against fatal doses of streptococci. A large group of sulfonamide drugs was soon made and used widely in treatment of infectious diseases. A few investigators notably DuBos in America and Chain and Florey in England searched for bacterial antagonists produced by natural enemies of bacteria occurring in Nature. DuBos[5] in 1939 developed in soil a bacterium which following autolysis inhibited the growth of a variety of gram-positive bacteria *in vitro,* and under stated conditions afforded a high degree of protection to mice inoculated with virulent pneumococci. Three active substances were prepared from the bacterial autolysate. They are named *tyrocidine hydrochloride, gramicidin,* and *tyrothricin*[6]. All three substances show clear cut inhibition to gram-positive bacteria *in vitro.* Unfortunately they are injurious to some animal cells, particularly the red blood cell; hence, clinical use of these drugs is of limited value.

In 1940 Chain, Florey and associates[7, 8] cooperated with Fleming in studying the therapeutic value of penicillin. It was quickly appreciated that in penicillin a substance had been found which had heretofore unexcelled bacteriostatic power, particularly in regard to staphylococci, streptococci, gonococci, and clostridia. Moreover, its index of toxicity to living cells was very low. War casualties required large quantities of a drug such as this be made available, and within a short time huge quantities were produced in this country.[9, 10]

The search for new antibiotics continued (Table I). Schatz, Waksman and Bugie[11] found that *Actinomyces griseus* elaborated a substance which inhibited *in vitro* the growth of gram-negative bacteria. This substance they named streptomycin. Other antibacterial substances have been found, among them streptothricin,[12] flavicidin[13] and subtilin.[14] These substances are not in use currently to treat disease in man because they are poisonous, or they have no advantage above those in use.

## USE AND LIMITATIONS OF ANTIBIOTICS IN INFECTIOUS DISEASES

The recognition of disease leads to proper application of remedies, and other means failing wisely provides for termination of useless treatment. Penicillin and sulfonamides are widely used and not always wisely. The indiscriminate use of these substances in fevers of obscure etiology is to be condemned, for reasons which are obvious. When small doses of these drugs are given there is the risk that

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TABLE I
SOME ANTIBIOTIC AGENTS OF MICROBIAL ORIGIN

| Antibiotic Agent | Microbial Derivation | Investigator | | Microbial Antagonism |
|---|---|---|---|---|
| Pyocyanase | Ps. Aeruginosa | Emmerich and Loewe (2) | 1899 | Gram + and Gram — bacteria |
| Pyocyanine | Ps. Aeruginosa | Wrede and Strach (26) | 1924 | Mainly Gram + |
| Penicillin | P. notatum Westling | Dubos<br>Fleming (3) | 1929 | Gram + Cocci and bacilli<br>Gram — cocci |
| Gramicidin<br>Tyrothricin<br>Tyrocidine | B. brevis | Dubos (5)<br>Hotchkiss and Dubos (6) | 1939<br>1940 | Gram + bacteria, mainly |
| Streptothricin | Actinomyces lavendulae | Waksman and Woodruff (12) | 1942 | Gram + and Gram — bacteria |
| Flavicidin | Aspergillus flavus | McKee, Rake and Hauck (13) | 1944 | Similar to penicillin |
| Streptomycin | Actinomyces griseus | Schatz, Bugie and Waksman (11) | 1944 | Gram negative bacteria |
| Subtilin | B subtilis | Salle and Jann (14) | 1945 | ? |

sensitive strains will be weeded out and a heartier race of bacteria survive to resist large doses of these drugs. Also in grave infections with apparently trivial onset the administration of antibiotics may obscure the true nature of the infection and valuable time is lost in instituting proper treatment.

The use of antibiotics in the treatment of infectious diseases should be supported by bacteriological studies. These studies must be directed by the clinician in order that the bacteriologist may know how to start his search. Cultures of body exudates and discharges, and blood cultures reveal pertinent and occasionally surprising information.

Moreover, it is necessary from time to time to determine the sensitivity of the infecting organism to sulfonamides, penicillin and streptomycin. This is not always essential, since the range of sensitivity of organisms to these drugs has been explored, and the dose necessary to control infection caused by susceptible organisms known, at least in part. Bacteria become resistant for reasons to be stated later. Hence, when the patient is not responding as expected, it may be informative to know the sensitivity of the bacterium causing illness. It may be desirable also to learn what concentrations of these drugs are present at a given time in the blood stream. Simple methods for these determinations will be described.

### UNITS OF PENICILLIN AND STREPTOMYCIN

The Oxford unit of penicillin is the smallest amount dissolved in 50 cc of meat extract broth which completely inhibits the growth of a susceptible strain of *Straphylococcus aureus* (Heatley Strain).[8] This amount is exceedingly small (0.6 microgram). Expressed differently, a meat extract broth containing 1 unit of penicillin per mg. just inhibits the growth of *S. aureus* in dilution of 1:50,000.[15] Penicillin preparations currently supplied for clinical use have a potency of from 100 to 1000 units per mg. An international unit has been proposed which has been defined as the specific penicillin activity contained in 0.6 micrograms of the International Penicillin Standard. This unit is approximately equal to the original Oxford unit.

The original unit of streptomycin was the smallest amount inhibiting the growth of a suitable culture of *Esch. coli* in 1 cc of broth medium. The National Research Council has stated the official unit to be the amount contained in 1 microgram of streptomycin base which is equivalent to 1 original unit. Hence, the dosage of streptomycin is expressed in terms of weight in which 0.010 gm. equals 10,000 units, 0.10 gm., 100,000 units and 1.0 gm. equals 1,000,000 units of streptomycin.

### DETERMINATION OF SENSITIVITY OF BACTERIA TO PENICILLIN AND STREPTOMYCIN

*Penicillin.* There are several methods.[16, 17, 18] In our laboratory, unless growth conditions are contrary, the method used[18] to determine sensitivity of bacteria to penicillin follows.

Prepare a standard solution of penicillin to contain 20 Oxford units per cc. The standard solution can be kept for a week if refrigerated. For daily tests prepare a secondary standard to contain 0.2 units per cc. The secondary standard is dispensed in the following amounts into 2 sets of Wasserman tubes, 0.05, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8 and 1.0 cc. To all tubes add brain heart infusion broth so that the volume in each tube is 1.0 cc. To one set of tubes add 2 cc of a 1:100 dilution of a standard strain of *B. subtilis*.[1] The sensitivity of this organism to penicillin is of the same order as most strains of hemolytic streptococci requiring as little as 0.0085 units per cc to inhibit a 1:100 dilution of broth culture. To the remaining set of tubes add 2 cc of a 1:100 (this dilution depends on amount of growth occurring in 18 to 24 hours at 37° C) dilution of a broth culture containing the bacterium in question. The concentration of penicillin in the tubes ranges from 0.0035 to 0.065 units per cc. Two control tubes containing 1.0 cc of broth should be inoculated with 2.0 cc of diluted standard and test bacteria. Incubate at 37° C. overnight. The last tube in which no growth occurs is taken as the endpoint. If an endpoint is not reached in the last tube, a second test is run using concentration of penicillin ranging from 0.05 to 20.0 units per cc. If the test organism is a pneumococcus, or streptococcus, usually the endpoint will be less than 0.06 units per cc. Alpha streptococci, enterococci and straphylococci may require higher levels (0.5 to 40 units) to inhibit growth. A method other than this one must be used to test the sensitivity of gonococci and meningococci to penicillin.

*Streptomycin.* There are also several methods.[19, 20] Price, Nielson and Welch[20] have described a simple method which requires materials and technique available in a small laboratory.

Prepare a standard solution of streptomycin to contain 100 micrograms per cc. Prepare a secondary standard to contain 10.0 micrograms per cc. The secondary standard is dispensed in the following amounts to 2 sets of Wasserman tubes 0.05, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, and 1.0 cc. To all tubes add a medium consisting of peptone 1 per cent, beef extract 0.5 per cent and sodium chloride 0.25 per cent adjusted to pH 8.0 with NaOH, sufficient to bring the initial volume in each tube to 1 cc. To one set of tubes add 2 cc of a 1:100 dilution of *B. circulans*.[2] This organism is sensitive to 0.15 micrograms per cc of streptomycin base. To the remaining set of tubes add 2 cc of a 1:100 dilution of the bacterium in question (grown 24 hours at 37° in medium noted above). The concentration of streptomycin ranges between 0.16 to 3.3 micrograms of streptomycin per cc. Two control tubes are inoculated also with known and unknown bacterial strains. Incubate at 37° C overnight. The last tube in which no growth occurs is taken as the endpoint. If an endpoint is not reached, a second test is run using concentrations of streptomycin ranging from 1.0 to 500 units. The growth of bacteria susceptible to strep-

1 The standard strain of B. subtilis grows exceedingly well at 30° C producing a diffuse turbidity in 24 hours. Its sensitivity is maintained over long periods of time without the necessity of repeated transfers. Cultures maintained at room temperature in screw cap bottle do not lose sensitivity for as long as 6 months.

2 The standard strain *B. Circulans* grows well at temperatures between 30 and 37° C. Broth cultures are stable. The microorganisms may be preserved in screw cap bottle (6°C) for a month without appreciable loss of sensitivity (20). Floccules form which make the endpoint in the serial dilution test easy to determine.

tomycin may or may not be inhibited by 5 micrograms. Resistance is met with and large concentrations may be required to establish an endpoint. One other disadvantage to this method is that it cannot be used to test sensitivity of members in the brucella and pasteurella group of organisms. Most laboratories prefer not to deal with these organisms, for the hazard of workers becoming infected is great.

### THE ESTIMATION OF PENICILLIN AND STREPTOMYCIN IN BODY FLUIDS

Simple methods for estimating the concentrations of penicillin and streptomycin in body fluids are in use.[18, 20] In the small hospital where trained persons and special equipment are not always available these methods are practical and useful. Other tests have been used.[16, 19] These are somewhat more complex. In these tests, described below, the standard organisms are those mentioned earlier in sensitivity tests, namely *B. subtilis* and *B. circulans.*

*Penicillin.* Prepare a standard solution of penicillin to contain 1 unit per cc of broth. Set up 2 rows of Wasserman tubes in series of 9 tubes. Additional series of tubes may be added if there is more than one sample or type of body fluid to be tested. To all except the first tube in each row add 0.5 cc of brain heart infusion broth. To the first tube add 0.5 cc of body fluids, namely serum, urine, cerebrospinal fluid, etc. To the second tube add 0.5 cc also. Mix well, then two-fold dilutions are made by adding 0.5 cc in series discarding 0.5 cc from the 9th tube. The standard solution of penicillin is added to one row of tubes. This 1 unit standard is diluted exactly as above in serial two-fold dilution. Add to each tube 1.5 cc of a 1:100 dilution of *B. subtilis* in broth. Incubate all tubes at 37° C overnight. The last tube in which no growth occurs is taken as the endpoint. This is very sharp; one tube will be clear whereas the next in series will have a typical pellicle of *B subtilis* on the surface of the media.

In reading the test the concentration is then determined by comparing the endpoint of the unknown with that of the standard. An example* taken from Randall, Price, and Welch's paper[18] follows.

| | Tube No. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Fluid | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Standard | 0 | 0 | 0 | 0 | 0 | 0 | + | + | + |
| Serum | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + |
| Urine 1:10 | 0 | 0 | 0 | 0 | + | + | + | + | + |

*From Randall, Price and Welch, Science 101:365, 1945.

The standard caused inhibition in the 6th tube. This represents the effect exerted by 1 unit of standard penicillin.[21] Serum caused inhibition in the 7th tube hence contains twice the amount referable to the standard, namely 2 units. The urine, diluted 1:10 was inhibited in the 4th tube, equivalent in reference to the standard to 0.25 units x10, or 2.5 units. Randall, Price and Welch state that the test can be used to determine levels as low as 0.03 units per cc. To determine levels lower than this is necessary to vary the dilution series of both standard and unknown.

Inhibitory substances may be present in serums and interfere with growth of *B. subtilis.* To detect these inhibitory substances a control set of tubes is run with each test. Serum should be inactivated at 56° C for 30 minutes. Add 0.2 cc of penicillinase to 5 cc of serum. A row of tubes containing serial dilution of serum exactly as outlined in the test is set up. To each tube in the control series add 1.5 cc of 1:100 dilution of *B. subtilis.* Incubate at 37° C overnight. Lack of growth in one or more of the tubes in this series reveals the concentration of inhibitory substances.

*Streptomycin.* The method is that of Price, Nielson, and Welch.[20] Prepare a standard solution of streptomycin salt of known potency to contain 10 micrograms per cc. In making dilutions of body fluids and of the standard procede as outlined under the method described for penicillin. Do not use brain heart infusion broth; use a modified medium (peptone 1 per cent, beef extract 0.5 per cent, and NaCL 0.25 per cent, pH 8.0) as diluent and culture medium. Add to each tube 1.5 cc of a 1:100 dilution of *B. circulans.* Incubate overnight. The last tube in which no growth occurs is considered the end point.

The concentration of streptomycin in the unknown is determined by comparing the endpoint with that of the standard. An example* follows.

| | Tube No. | | | | | | |
|---|---|---|---|---|---|---|---|
| Fluid | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Standard | 0 | 0 | 0 | 0 | 0 | + | + |
| Serum | 0 | 0 | 0 | + | + | + | + |
| Urine 1:50 | 0 | 0 | 0 | 0 | + | + | + |

*From Price, Nielson, and Welch, Science 103:56, 1946.

Growth is inhibited in the standard in the 5th tube. This represents the effect exerted by 10 micrograms of streptomycin. The serum inhibited growth in the 3rd tube, and is ¼ as effective as the standard, hence contains 215 micrograms. The urine caused complete inhibition

TABLE II

SUSCEPTIBILITY OF BACTERIA TO PENICILLIN AND STREPTOMYCIN

| PENICILLIN | | STREPTOMYCIN | |
|---|---|---|---|
| *Highly Susceptible* | *Moderately Susceptible* | *Highly Susceptible* | *Moderately Susceptible* |
| Staph aureus | Str. faecalis (Group D) Lancefield | Esch. coli† | N. gonorrheae* |
| Str. hemolyticus Group A, B, C. | Str. viridans | Esch. communior† | D. pneumoniae* |
| D. pneumoniae | Anaerobic Streptococci | Aerobacter aerogenes† | Str. faecalis* |
| N. intracellularis | Actinomycoses bovis | Br. abortus** | Str. viridans* |
| N. gonorrhoeae | $C_1$. botulinum | Br. suis** | Sal. suipestifer |
| H. ducreyi | Spirillum minus | Br. melitensis** | Malleomyces mallei |
| C. diptheriae | Leptospira icterohemorrhagica | H. influenzae† | E. typhi* |
| $C_1$ tetani | *Psittacine Viruses | H. pertussis* | |
| $C_1$ oedematiens | | P. tularense | |
| $C_1$ welchii | | Sal. enteritidis | |
| B. anthrax | | Sal. typhimurium | |
| Treponema pallidum | | Sal. schottmullerei | |
| | | M. tuberculosis (human)* | |
| | | K. pneumoniae | |

* clinical value awaits more study.
** does not bring about cure: remissions occur.
† may quickly develop resistance to the drug.
Taken from Kolmer, J. A., Penicillin Therapy, 1945 D. Appleton, Century Co.

in the 4th tube, is half as effective as the standard, hence contains 5 micrograms; since it was diluted 50 times, the original sample contains 250 micrograms. It is not necessary to use a control series for the demonstration of naturally occurring inhibitory substances in serum to *B. circulans*. Thus far inhibitory substances have not interfered with the test.

### ACTION OF PENICILLIN AND STREPTOMYCIN AGAINST BACTERIA

*Susceptible Bacteria.* A wide variety of infections is caused by bacteria against which penicillin and streptomycin are fully effective. Some of the bacteria susceptible to these drugs *in vitro* are listed in Table II.

There is wide variation in the sensitivity of bacteria to penicillin and streptomycin. Members of alien races differ in resistance to these drugs; members in the same tribe and species are unequal in sensitivity to streptomycin and penicillin (Table III). To some extent this difference in susceptibility of bacteria to antibiotics explain differences in therapeutic response.

In addition to *natural resistance* among strains of bacteria there is the problem of induced or acquired resistance. Resistance to the action of penicillin has been induced in organisms which were initially sensitive to the drug by growing them in a medium in which the concentration of penicillin is progressively increased.[22, 23, 24] Resistance to penicillin has been developed by strains of *Staph. aureus*,[22] *Str. hemolyticus*, and *N. gonorrhoeae*,[25] among others. In a similar manner strains of gonococci and meningococci have become resistant following repeated transfer in increasing concentrations of streptomycin. Of much more serious nature has been the clinical experience that strains of staphlococci develop resistance during treatment with penicillin. Strains of coli-aerogenes bacilli may quickly become resistant to streptomycin. At this time susceptible strains of bacteria appear to develop resistance to streptomycin more easily and speedily than they do to penicillin.

The manner in which staphylococci acquire resistance to penicillin has been studied by De Merec.[22] His observations indicate that even very susceptible strains of staphylococci give rise to a few variants resistant to small concentrations of penicillin. As these variants grow they give rise to other variants of higher resistance. In several steps, but never in one step, it is possible to obtain variants resistant to concentrations as high as 250 or more units per cc. This type of resistance is usually permanent, although Spink[27] has observed resistant strains to become sensitive ones. Using a statistical method, DeMerec was able to show that these penicillin-fast variants arise by rare mutations from sensitive organisms. Such mutants are not dependent on the presence of penicillin, the presence of the latter merely exposing their existence.

Bacteria develop resistance to streptomycin also. The mechanism whereby resistance is developed is not known. It is not unlikely that similar mechanisms operate in the development of resistance to penicillin and streptomycin. In addition to developing resistance to antibiotics, some bacteria elaborate an enzyme, *penicillinase* which destroys the growth inhibiting factor of penicillin. This enzyme may be found in penicillin-sensitive strains of bacteria. Some strains of staphylococci[23, 27] apparently produce this enzyme; these strains may not respond to treatment with penicillin.[23] Lawrence[28] has pointed out that a diastatic enzyme *clarase* also possesses powerful inhibitory effect on penicillin. Similar enzyme systems inhibiting the action of streptomycin probably exist, although evidence of their presence is yet to be uncovered.

### METHODS OF ADMINISTRATION

Penicillin is available in vacuum packed ampules containing 5000, 10,000, 25,000, 100,000 and 1,000,000 units. The drug is soluble in distilled water, normal salt solution, and 5 per cent dextrose. It is available also incorporated in beeswax and peanut oil (see below).

Streptomycin is dispensed either as the sulphate or hydrochloride, in ampules containing 1. Gm. of the salt. The drug is soluble in distilled water or normal salt solution.

The routes of administration of these two drugs are outlined in Table IV.

Penicillin and streptomycin may be installed into joint, abscess and empyemal cavities when the in-

TABLE III

RANGE OF IN VITRO SENSITIVITY OF BACTERIA TO PENICILLIN AND STREPTOMYCIN

| PENICILLIN | | STREPTOMYCIN | |
|---|---|---|---|
| *Bacteria* | *Oxford Units Per CC.* | *Bacteria* | *Micrograms Per CC.* |
| Staph. aureus | 0.02-5.0 | Esch. coli | 0.3-256 |
| Str. hemolyticus, Group A | 0.0078-0.2 | A. aerogenes | 0.5-256 |
| "Green Streptococci" | 0.02-5.0 | E. typhi | 1.0-75 |
| Enterococci, Group D | 0.01-40.0 | K. pneumoniae | 0.15-256 |
| N. meningitides | 0.016-0.5 | H. influenzae | 0.08-10.8 |
| N. gonorrhoeae | 0.002-0.176 | H. pertussis | 1.25-5.0 |
| D. pneumoniae | 0.008-0.063 | P. tularensis | 0.15-3.0 |
| H. ducreyi | 0.06-0.13 | Brucella group | 0.10-0.5 |
| H. hemophilus | 0.031-0.50 | M. tuberculosis (human) | 0.15 |
| | | Salmonella | 0.5-200 |

fection of these spaces is caused by sensitive strains of bacteria. These drugs may be applied to mucous membranes of the nose, accessory nasal sinuses and middle ear.

Romansky and associate[29,30,31] have tried to prolong the absorption and hence the duration of therapeutic levels of penicillin in the circulating blood. The effort has resulted in suspending calcium penicillin in beeswax and peanut oil. The standard preparation which would maintain therapeutic levels of penicillin (0.6-125 Oxford units per cc) for about 24 hours after a single injection is in the adult 300,000 units of calcium penicillin in 4-8 per cent beeswax in peanut oil contained in 1.0 cc. Penicillin-beeswax-peanut oil mixture has proved effective in the treatment of gonorrhea, pneumococcal pneumonia, and in staphyloccic and streptococcic infections. It should not be used alone in fulminating infections.

### ABSORPTION AND EXCRETION OF PENICILLIN AND STREPTOMYCIN

*Penicillin.* The fate of penicillin administered through various portals has been studied.[3,30,32,33,34] Following a single intravenous injection of 5000 to 40,000 units the peak concentration in the blood (0.156-2.5 units per cc) is reached in a few minutes and falls rapidly during the ensuing three hours

TABLE IV

ROUTES OF ADMINISTRATION OF PENICILLIN AND STREPTOMYCIN

| *Route of Administration* | *Advantages and/or Disadvantages* | |
|---|---|---|
| | *Penicillin* | *Streptomycin* |
| ORAL | Absorption is irregular.<br>Blood concentration is poorly maintained.<br>Dose = 3 — 5 times intramuscular requirements<br>500,000-3,000,000 units necessary for good levels. | Very little if any absorbed in blood.<br>Destroys susceptible bacteria in gut.<br>2-3 Gm. daily required.<br>Useless in systemic infections. |
| INTRAMUSCULAR | Best route for general use.<br>Maximum serum levels 30 min. to one hour.<br>Requires injection at 3 hr. intervals at most.<br>Dose range 5000-30,000 units; in Beeswax containing 300,000 units 1 dose in 24 hours. | Usual route of administration.<br>Maximum serum levels occur in 1-3 hours.<br>Addative effects obtained with injections at 3 or 4 hour intervals.<br>Painful: procaine may be used. |
| INTRAVENOUS | Used in severe infections, septicemia, endocarditis, etc.<br>Given along with intramuscular route or by continuous intravenous drip.<br>May be given in isotonic saline or 5% dextrose.<br>In continuous drip give at rate 30-40 drops min., 20,000 to 80,000 units per liter. | Seldom used; no advantage over intramuscular route.<br>May produce unconsciousness if given rapidly. |
| INTRATHECAL | Generally 10,000 units every 12 hours is given.<br>Dose=1000 units per cc of isotonic saline.<br>Intravenous or intramuscular route also used.<br>Good levels persist 12 to 24 hours. | 25,000 to 100,000 units every 24 hours is given.<br>Dose is made up in 5 to 10 cc of saline.<br>Intramuscular therapy used also.<br>Good levels persist 24 hours or longer. |
| AEROSOLS | An aqueous solution of penicillin containing 50,000 units per cc is nebulized by passing 8 liters of $O_2$ thru it per minute.<br>Good levels, 4.0 units per cc (serum) can be achieved. | Concentrations of 50,000 units per cc may be inhaled to a total amount of 500,000 units in 24 hours.<br>Little streptomycin is absorbed from the lung. |

TABLE V

MEAN CONCENTRATIONS OF PENICILLIN AND STREPTOMYCIN IN BODY FLUIDS FOLLOWING ADMINISTRATION THROUGH SEVERAL PORTALS AND WITH VARYING DOSES.*

| *Portal of Administration* | *Dose Oxford Units* | *CONCENTRATION OF PENICILLIN PER CC OF SERUM* | | | | | | *CONCENTRATION OF STREPTOMYCIN PER CC OF SERUM* | | | | | | *DOSE UNITS 1 unit = 0.1 micro gram* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *5 min.* | *30 min.* | *1 hr.* | *2 hrs.* | *3 hrs.* | *4 hrs.* | *15 min.* | *30 min.* | *1 hr.* | *2 hrs.* | *4 hrs.* | *6 hrs.* | |
| 1. ORAL | 25,000 | 0.02 | 0.02 | 0.1 | 0.02 | ..... | 0.39 | 0 | 0 | 0 | 0 | 0 | | 1,000,000 |
| | 300,000 | ..... | 2.0 | 2.0 | 0.50 | 0.10 | 0.04 | | | | | | | |
| | 5,000,000 | ..... | 10.0 | 10.0 | | ..... | 0.04 | | | | | | | |
| 2. INTRAMUSCULAR | 10,000 | 0.039 | 0.078 | 0.078 | 0.039 | ..... | ..... | 0 | .. | 3.0 | 0 | 0 | .. | 40,000 |
| | 20,000 | ..... | 1.0 | 0.6 | 0.1 | ..... | ..... | .. | .. | 11.0 | 8.0 | 5.0 | | 200,000 |
| Adults | 50,000 | ..... | ..... | 0.960 | 0.48 | ..... | ..... | 6.0 | .. | 10.0 | 4.0 | 8.0 | .. | 400,000 |
| | 60,000 | 0.60 | 1.4 | 1.0 | 0.20 | ..... | ..... | 8.0 | .. | 6.0 | 16.0 | 14.0 | .. | 500,000 |
| | 5,000 | ..... | 1.6 | 0.8 | ..... | ..... | ..... | .. | .. | 17.0 | 17.0 | 16.0 | 9.0 | 600,000 |
| Infants | 10,000 | ..... | 1.4 | 0.6 | ..... | ..... | ..... | | | | | | | |
| Peanut-oil beeswax mixture | 100,000 | ..... | ..... | ..... | 0.312 | 0.312 | 0.312 | | | | | | | |
| | 200,000 | ..... | ..... | 0.625 | 0.625 | 0.625 | 0.625 | | | | | | | |
| | 300,000 | ..... | ..... | ..... | 0.625 | 2.0 | 1.25 | | | | | | | |
| 3. INTRAVENOUS | 10,000 | 0.625 | 0.078 | 0.039 | 0 | 0 | ..... | 6.0 | .. | 3.0 | 0 | 0 | .. | 50,000 |
| | 20,000 | 1.250 | 0.312 | 0.078 | 0.015 | 0 | ..... | 22.0 | .. | 8.0 | .. | .. | 3.0 | 200,000 |
| | 40,000 | 2.50 | 0.156 | 0.078 | 0.010 | 0 | ..... | 32.0 | .. | 12.0 | 8.0 | .. | 6.0 | 400,000 |
| | 60,000 | 2.00 | 1.40 | 0.40 | 0.20 | 0 | ..... | 47.0 | .. | 22.0 | 14.0 | .. | 10.0 | 500,000 |
| | | | | | | | | 32.8 | 29.0 | 27.0 | 20.0 | 10.0 | 15.0 | 600,000 |
| | | *CONCENTRATION PER CC OF CSF FLUID* | | | | | | *CONCENTRATIONS PER CC OF CSF FLUID* | | | | | | |
| | | *6 hrs.* | *15 hrs.* | *24 hrs.* | *38 hrs.* | *36 hr* | | *15 min.* | *30 min.* | *1 hr.* | *2 hrs.* | *3 hrs.* | *24 hrs.* | |
| 4. INTRAVENOUS | | | | | | | | | | | | | | |
| 5. INTRATHECAL | 10,000 | 5.0-25.0 | 0.156 | 0.156 | 0.19 | ..... | | .. | .. | .. | 0 | 0 | 0 | 500,000 |
| | | | | | | | | | | | | 13.2 | | 750,000 |
| | | | | | | | | | | | | | 0.9-25.0 | (TBC meningitis) |
| | | | | | | | | | | | | | | 10,000† |

*Compiled from Reports in the literature (39, 40, 41, 42, 43, 44, 45)

(Table V). With large doses (20,000 units) detectable quantities of penicillin remain in the blood longer than with smaller doses. If penicillin is administered by continuous intravenous drip (50,000 units over each 3 hour interval) a fairly constant serum level of 0.20-0.30 units per cc can be maintained. Single intravenous injections given every three hours do not provide adequate concentration to stop bacterial growth during the entire interval between injections.

Following intramuscular injection maximum blood concentrations are reached more slowly, usually in one or two hours. These levels arise more slowly and are maintained longer than is the case in intravenous administration. Penicillin can be injected into body cavities, such as knee joint and pleural space. Such administration is followed by slow local absorption and delayed excretion; the local concentration of penicillin is effective for 10 to 20 hours.

Penicillin does not enter the cerebrospinal fluid following intravenous or intramuscular doses ranging from 10,000 to 30,000 units. Although this appears to be true in healthy subjects, in persons with meningitis penicillin may be detected in the cerebrospinal fluid (0.03-0, 35 units per cc) following parenteral administration. The experience of Rammelkamp and Keefer indicates that intrathecal administration of penicillin (10,000 units) in a normal person results in a concentration of 25 units per cc 6 hours later. The level then falls rather sharply so that at 18 hours very little penicillin can be detected in the spinal fluid. In patients with meningitis to whom the drug has been given intrathecally there is more rapid absorption of penicillin from the spinal fluid; appreciable quantities may be found in the blood for as long as 18 hours following intrathecal administration.

Penicillin is destroyed in the stomach. If huge doses (300,000 to 5,000,000 units) are given by mouth appreciable levels (1.25-20.0 units) can be detected in the blood in 20 or 30 minutes.[34] This is considerable individual variation in absorption of the drug. It would appear that about ⅓ of the total dose is absorbed; the remainder must be destroyed or excreted. Failure of maximum absorption from the small intestine is stated to be responsible for relatively insufficiency of the oral route.

Penicillin is absorbed freely from the lung during inhalation of aerosols. Blood levels as high as three or four units of penicillin per cc have been obtained.

Penicillin is excreted in large part by way of the kidneys. Following intravenous administration of penicillin almost all appears in the urine within an hour. The percentage of the administered dose excreted in the urine varies. In normal adults the variation ranges from 37 to 99 per cent. The amount excreted probably depends upon the route of administration and dosage. Some penicillin fractions are inactivated by various living tissues.[35] Renal disease delays excretion.

*Streptomycin.* The blood level of streptomycin following a single intravenous injection is maintained at a higher level for a longer period of time than is the case with penicillin.[36] Following intravenous injection of 200,000 to 400,000 units (0.2-0.4 Gm.) 5 to 10 units per cc of circulating blood is still present at the end of 4 hours, representing roughly a fourth of the dose administered. As for penicillin none can be detected in the blood at a corresponding period following intravenous administration.

The concentration of streptomycin in the blood following intramuscular injection does not reach the high value observed following intravenous injection (Table V). During the ensuing three hours, the dosage remaining constant blood concentrations reach corresponding levels regardless of whether the drug is given intramuscularly or intravenously. If streptomycin is administered every three hours an addative effect is observed.[37]

Streptomycin, like penicillin does not enter the cerebrospinal fluid following parenteral inoculation (50,000 units) in patients who do not have meningeal disease. Like penicillin, however, streptomycin can be detected in appreciable concentration in the spinal fluid of children with meningitis.[38]

Streptomycin given orally is poorly absorbed, and most of the drug appears in the feces. When large doses (1.0 Gm) are given daily small amounts (one to six units per cc) may be found in the blood. Hence, very little is found in the urine. The stool concentration varies from 1,000 to 5,000 units per Gm. of feces.[38]

Streptomycin diffuses into body transudates and exudates. It enters fetal cord blood and amniotic fluid. Sometimes diffusion is slow (6 units in 2 hours following 600,000 units intravenously). A corresponding dose given to patients with perforated peptic ulcers has provided within 2 hours good concentrations of streptomycin (17.8 to 22.0 units) in peritoneal fluid.[36]

When administered parenterally streptomycin is excreted for the most part unchanged in the urine. There is wide variation in the amount excreted. With large doses (0.5 Gm) 41 to 92 per cent in the urine within 24 hours. Streptomycin is excreted slowly as compared with penicillin. Only about two per cent of the drug appears in the feces. It appears that some streptomycin is destroyed or retained in the body.

### TOXICITY OF PENICILLIN AND STREPTOMYCIN

*Penicillin.* No significant toxic effects have been noted following systemic therapy with the sodium or calcium salt of penicillin. The most common complication is urticaria. Urticarial wheals appear between the fifth and tenth day of treatment. These may be benefited by epinephrine or benedryl. There may be a transient azotemia. Thrombophlebitis occurs during continuous intravenous medication. The intrathecal injection may produce headache, vomiting and pleocytosis.[39] Walker[40] among others notes that penicillin given intrathecally can cause changes in the arachnoid, alter nerve fibers and produce radiculitis. Convulsions may occur.

*Streptomycin.* A number of toxic reactions have been noted following parenteral injection of streptomycin. Among these are flushing of the skin, and a sense of fullness shortly after injection of the drug. Headache, transient urticaria and fever may occur also. Buggs *et al*[36] report two patients who lost consciousness following rapid intravenous injection. Recovery occurred in a few minutes. Thrombophlebitis occurs. There may be generalized aches and pains in the joints. Fatty metamorphoses in parenchymal cells of the liver and the tubular epithelium of kidneys have been seen in experimental animals.[41] Eighth nerve deafness has occurred also[42]. When the dosage in adults is kept under 1.0 Gm. daily, few reactions occur.

### CLINICAL USE OF PENICILLIN AND STREPTOMYCIN

Penicillin is a drug possessing herculean ability to combat infection caused by a number of bacteria. It is not a panacea for all of the infectious diseases; its use in serious illness is based on an understanding of the underlying disease process. Of itself, it cannot promote healing except by bringing to a halt bacterial growth. By retarding bacterial growth the normal defense and reparative mechanisms of the body are mobilized.

*Staphylococcic Infections. Staph. aureus* causes infections in man more often than *Staph albus.* Among the infections caused by staphylococci are cellulitis, osteomyelitis, cavernous sinus thrombosis, meningitis, endocarditis, and sepsis. Results achieved with the use of penicillin in these pathological states have been good compared with all earlier forms of treatment. The *in vitro* sensitivity ranges from 0.08 to 5.0 units of penicillin per cc. Some strains become resistant to the drug; others may liberate a substance inhibiting the action of penicillin. Prognosis is influenced by the duration of illness prior to treatment as well as acccessibility of a supperative focus of infection.

In staphylococcic infections large initial doses are preferred, particularly if bacteremia is suspected and confirmed by cultures. The focus of infection should be sought after, and, if accessible to surgery, drained. In children the total daily dose adequate for most infections is stated[43] to be for infants 20,000 to 40,000 units, for larger children 60,000 to 80,000 units. In overwhelming sepsis 100,000 to 150,000 units may be needed. In infants who are in shock intravenous administration of penicillin is imperative. In infants and children who are not in shock intramuscular injection is the method of choice. In adults with staphylococcic bacteremia a daily dose of 200,000 to 400,000 units is used to bring the infection under control[44]. In meningitis the drug is given intrathecally and intramuscularly.[3] Sulfonamides may be given also to arrest growth of penicillin-resistant staphylococci. Penicillin is instilled into staphylococcic empyema cavities and infected joint spaces. In acute hematogenous osteomyelitis penicillin is very effective. The lesions heal but may recur. In chronic osteomyelitis the results have not been so impressive. The presence of sequestra delays the clearing up process. Surgical care may be necessary in such cases. Calcium penicillin in beeswax and peanut oil is used in the treatment of furuncles and abscesses.

The use of penicillin in staphylococcic infections with bacteremia has reduced the mortality rate. About 90 per cent of these patients, all ages considered, died in the days preceding the sulfonamides. The mortality rate is still about 30 per cent. Among children ill with hematogenous osteomyelitis 10 to 50 per cent died; now the mortality rate is less than 5 per cent. In general children suffering from staphylococcic infections appear to respond to treatment better than do adults.

*Streptococcic Infections.* Among all the streptococci, the hemolytic streptococcus is the chief offender in man. Among the infections caused by this organism are tonsillitis and pharyngitis, scarlet fever, pneumonia, meningitis, pericarditis, arthritis, and sepsis. Complications of these diseases are otitis media, mastoiditis, empyema, and cavernous sinus thrombosis. The results of treatment of these conditions with penicillin have been good. The *in vitro* sensitivity of most streptococci ranges from 0.008 to 0.2 units of penicillin per cc. Most streptococci infections in adults respond to 100,000 units of penicillin given daily. In children 20,000 to 60,000 units generally will be enough to control infection with this bacterium.

Penicillin is superior to sulfonamides in the treatment of infections caused by the hemolytic streptococcus. These bacteria are relatively sulfonamide resistant as compared with pneumococci, meningo-

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3 Some students of infectious diseases do not belive it necessary to administer antibiotics into the subarachnoid spaces in treating purulent meninigitis. Whether to do so or not is not settled. It is clearly evident that other routes, namely intravenous and intramuscular, if they suffice to control these infections are to be desired.

cocci and staphylococci. Nevertheless, sulfonamides are of value in the treatment of otitis media, mastoiditis, meningitis and pneumonia of streptococcic origin. Blake[45] stated that sulfonamides should be used in less severe infections where there is tissue invasion without suppuration, necrosis and bacteremia. It is now reasonably clear that penicillin need not be reserved for severe infections; it may be used in mild streptococci infections also now that it is available.

Penicillin shortens the course and severity of streptotoccic pharyngitis. Plummer *et al*[46] have temporarily cleared the pharynx of streptococci in 24 to 48 hours following penicillin therapy. Recurrences occurred if the drug was stopped at this time. Young adults were given 15,000 units every four hours for six days. A lesser period of treatment failed to eradicate all hemolytic streptococci, and in some instances there was recurrent pharyngitis.

Penicillin is useful in the treatment of scarlet fever. With adequate treatment there is a prompt fall in temperature, and a reduction of toxic manifestations. Complications occur less often. The carrier state is of shorter duration[67]. Hoyne[68] points out, however, that scarlet fever is a mild disease now, and it is not entirely clear what the effect of penicillin will be in preventing the complications in severe scarlet fever.

Impetigo caused by *Str. hemolyticus* responds swiftly to parenteral or topical penicillin.

It is clearly evident that penicillin and sulfonamides have reduced the complications following streptococcic infections. Penicillin is superior to sulfonamides. If complicating lesions develop following untreated infection they may respond favorably with the use of chemotherapeutic substances. Not much is known concerning the prevention of late complications such as nephritis. Recent evidence[47,48,49] indicates that penicillin given prior to or during an attack of acute rheumatic fever does not prevent or cure it. Penicillin is not of value in the treatment of rheumatic fever.

*Bacterial Endocarditis.* Almost every known bacterium has been met with in endocarditis. Approximately 95 per cent of all cases is due to a streptococcus of the viridans or non-hemolytic type. Enterococci (Group D Streptococci) also cause endocarditis. Loewe and associates[50] distinguish an organism in endocarditis which they call streptococcus sbe. These cases are refractory to treatment. The average range of susceptibility of green streptococci is 0.2 to 5.0 units of penicillin per cc. Enterococci (*Str. faecalis*) are most resistant, being resistant at times to more than 40 units of penicillin per cc.

The successful treatment of bacterial endocarditis depends in part upon the duration of the disease and on the susceptibility of the offending organism to the drug. In this disease a constant drip of penicillin, preferably intravenously should be used[51]. In this way it is possible to maintain constantly inhibiting blood levels day and night. Some patients have done well when the drug was given by continuous drip whereas fractional intramuscular administration failed to clear the blood stream of bacteria. Whenever the bacterium is resistant to more than 0.5 units of penicillin per cc, large doses of penicillin should be administered by intravenous drip. Intramuscular injection may be resorted to, particularly if there is difficulty in entering veins, and in cases when the offending organism is quite sensitive.

The method of treatment used by Goerner, Geiger and Blake[51] seems to be the logical approach in treatment of this disease. The basic plan of treatment was to treat each patient with about 240,000 units of penicillin daily for three or four weeks. The penicillin was usually given by continuous intravenous infusion maintained day and night. A larger dose or longer course of treatment was dependent on the resistance (*in vitro*) of the infecting organism to penicillin, unsatisfactory serum penicillin levels, or unfavorable clinical course. The total quantities of penicillin in cured cases ranged from 3.9 to 17.4 million units, the number of days of treatment ranged from 20 to 70. The employment of massive doses in long courses and administration of the drug by a route making possible continued high titers of penicillin in the blood will, as a rule, bring the infection under control in most cases. The use of anticoagulants appears to be unnecessary.

In children with heart disease, acquired or congenital, it is advisable in extraction of teeth to give 100,000 units of penicillin one hour before and one hour after the operation. Penicillin may be used in prevention of complications following tonsillectomy in these individuals.

*Pneumococcic Infections.* Among the infections caused by the pneumococcus are pneumonia, empyema, otitis media, mastoiditis, meningitis, pericarditis, endocarditis and sepsis. In most instances these conditions respond quickly to treatment with penicillin. The average *in vitro* susceptibility to penicillin of pneumococcic is 0.04 units per cc. (range 0.008-0.063 units per cc.) The advance of pneumococcic infections is brought quickly under control in most cases by penicillin. Sometimes the infection is more or less refractory to penicillin. Sulfonamides are then used.

In pneumococcic pneumonia, 120,000 units daily for four to six days usually bring the infection under control. Bunn *et al*[52] have given penicillin

orally to patients with lobar pneumonia. An initial dose of 200,000 units followed by 50,000 units every two hours for seven days appears to halt inroads of the infection. It is well to bear in mind that pneumonia may not be pneumococcic in origin. In infants and in young children the influenzae bacillus (*H. influenzae*) may join the pneumococcus in producing bronchopneumonia. Such infections do not respond as expected with the use of penicillin. There are pulmonary infections caused by fungi, protozoa, rickettsiae, and filterable viruses, namely, histoplasmosis, toxoplasmosis, Rocky Mountain Spotted Fever and influenza. These infections do not respond to treatment with penicillin.

The treatment of post pneumococcic empyema should be governed jointly by internist and surgeon. Repeated thoracentesis may be done, reinjecting 15,000-30,000 units of penicillin. The objectives are sterilization of the exudate and obliteration of the space by re-expansion of the lung. In cases where the empyema fluid becomes sterile, there may be a delay in institution of surgical treatment to expand the lung. Surgery is always needed if the pleura becomes so thickened that the lung cannot re-expand.

Pneumococcic meningitis in infants and children is an extremely serious infection. It should be diagnosed quickly so that treatment can be started soon. Accurate bacteriological studies are imperative. The treatment of children by Hartmann[53] follows. Following collections of spinal fluid 20,000 units of penicillin in a volume of fluid somewhat less than that removed is injected into the arachnoid space; 10,000 to 20,000 units of penicillin is given intramuscularly. An initial subcutaneous dose of the sodium salt of sulfadiazine (0.5 per cent) is given subcutaneously. The sulfonamide is given along with ⅙ molar sodium r-lactate 30 cc. per kilogram body weight, if there are no signs or symptoms suggesting marked acid base balance change. Sodium lactate is used to produce an alkaline urine. Treatment is continued by subcutaneous injection of 0.1 Gm. per kilogram of sodium salt of sulfadiazine (0.5 per cent), every eight or twelve hours. Simultaneously with the administration of the sulfonamide ⅓ of the total potential alkali per 24 hours (10 cc. per kilogram of ⅙ M sodium lactate) is given. By this means high blood levels are attained quickly and perhaps precipitation of sulfonamide salts in the kidney tubule is prevented. Intrathecal and intramuscular injection of penicillin is continued. The number of times penicillin needs to be injected into the subarachnoid space depends on the examination of the spinal fluid, and the presence of pneumococci. Daily instillation of penicillin for one to eight days may be necessary. In some cases specific serum therapy may be needed to bring about arrest of the disease. Continued penicillin and sulfonamide therapy is necessary for ten days to two weeks or longer in less favorable cases. Sequelae such as hydrocephalus, epilepsy, and mental retardation, may be expected when infection occurs during infancy and early childhood and is not eradicated immediately[53].

*Gonococcic infections.* Among the infections caused by the gonococcus are arthritis, epididymitis and prostatitis in men, salpingitis and peritonitis in women, conjunctivitis and vaginitis in infants and children. This bacterium may cause endocarditis also. The gonococcus is very susceptible to the action of penicillin. Its *in vitro* sensitivity ranges between 0.002 to 0.176 units per cc. In uretheritis and vaginitis Romansky[31] cured 98 per cent of cases following a single intramuscular injection of calcium penicillin in beeswax and peanut oil. In uncomplicated cases 100,000 to 150,000 units of penicillin administered parenterally in divided doses will cure 90 to 98 per cent of all cases.

Penicillin is very effective in the treatment of gonococcic vaginitis and conjunctivitis in children. Infants with conjunctivitis may be cured with a total dosage of 50,000 units; 5000 units are given at three hour intervals. Vaginitis is treated with 100,000 to 125,000 units in fractional doses over a period of 24 to 48 hours.

Sulfonamides may not cure gonococcic infections. Some strains of gonococci become resistant to the action of sulfonamides. These cases may be treated successfully with penicillin. It is possible to induce resistance to penicillin in gonococci grown in the presence of increasing concentrations of the drug[25].

Experience has shown that in using penicillin to treat acute gonorrhea in patients who have been infected at the same exposure with syphilis, the latter may be masked and remain undetected for long periods.

*Meningococcic Infections.* Meningococcic infections respond satisfactorily as a rule to sulfonamides. Failure of the infection to respond favorably in 24 to 48 hours to the sulfonamides provides indication for the added use of penicillin. Patients receiving penicillin only may not do as well as with the use of sulfonamides.

*Syphilis.* The status of penicillin in the treatment of acquired syphilis has been reviewed recently by Dennie[54].

Congenital syphilis is a severe and complex disease and should be considered apart from the acquired syphilis of adults. In congenital syphilis there is a continual feeding of the spirochaetes to

the blood stream. The infection is massive[55] involves all organs, including bone. The infection is serious because of the rapid growth of tissues in the developing child. The most acute stages are seen during the first few months of life. During this period the mortality rate in untreated cases is high for two reasons, namely (1) the generalized syphilitic state is a forerunner of debility (2) and increased susceptibility of the infant to secondary infection.

Penicillin is effective in the prevention of prenatal syphilis, regardless of the duration of syphilis in the mother. Goodwin and Moore[56] propose the following minimum requirements. The total dose of penicillin is not less than 2.4 million units administered intramuscularly at two to three hour intervals night and day. The total duration of treatment should not be less than seven and one-half days. Following completion of penicillin treatment the mother should be followed clinically, and with quantitatively titered serologic tests at least once a month until delivery, as well as after the birth of the infant. A second treatment with penicillin should be given during pregnancy if there is (a) evidence of clinical or serologic relapse or (b) the original maternal serologic titer does not significantly decline within three months after treatment. In our present knowledge a pregnant syphilitic woman, although previously treated with penicillin should be treated again with penicillin in each succeeding pregnancy. The infant is followed for three to six months after birth by means of (a) physical inspection (b) quantitatively titered blood serologic tests, preferably every two weeks and (c) roentgenograms of the long bones taken at the first and sixth weeks of life.

The early treatment of infantile congenital syphilis with penicillin appears to be satisfactory. Final evaluation must wait for further data, specifically in respect to completeness of cure, and in general in respect to the efficiency of various fractions of penicillin[63]. Experience indicates that larger doses per kilogram body weight in infants are needed than that based on 2.4 million units for a 68 kilogram adult. If the latter dose is used 70 per cent of patients have their syphilitic infection arrested. Ingraham and associates recommend 75,000 units of penicillin per lb. body weight be given intramuscularly at three-hour intervals in a period not less than 15 days. Patients should be followed every month for the first six months, then at three month intervals for two years. Physical examination and quantitatively titered serologic tests should be carried out at each visit. X-rays of long bones are taken at the first and sixth week of life.

The treatment of late congenital syphilis is not satisfactory. Penicillin appears to be of no value in interstitial keratitis. No clinical improvement was observed by Wilkinson *et al*[57] in the treatment with penicillin of late congenital neurosyphilis.

*Other Uses for Penicillin.* Rat bite fever (*Spirillum minus*), anthrax, gas gangrene, among others respond favorably with the use of penicillin. Actinomycoses may be affected beneficially. Penicillin may be of value in treating diphtheria, but antitoxin should be used also, since penicillin is bacteriostatic and cannot affect circulating toxin. The use of penicillin in tetanus is not proved. Forgacs and Hutchinson[66] have reported on two strains of H. influenzae type b which were sensitive to penicillin. This drug has been used with some success in treatment of lung abscess, bronchiectasis and brain abscess. Careful consideration of its use in these conditions is desired, for surgical care may be delayed too long. Penicillin is a valuable drug in surgery particularly in controlling and preventing infections.

## STREPTOMYCIN

Streptomycin is a more recent antibiotic than penicillin. Its field of usefulness has been tested by many clinical investigators under the direction of the National Research Council. The entire range of usefulness of this drug has not been adequately explored, but, existent knowledge in view, streptomycin is not as good as penicillin for at least two reasons, namely (a) it is more toxic, and (b) bacteria quickly develop resistance to its action.

Microorganisms that are susceptible to the action of streptomycin vary widely in their sensitivity. As noted earlier, many strains of organisms initially susceptible to 5 or 10 micrograms of streptomycin per cc. often acquire resistance *in vitro* to enormous amounts of this drug. It has also been shown that in the presence of blood or serum the tolerance of bacteria to streptomycin may be increased 4 to 8 times. It is desirable then to maintain a concentration of streptomycin in the blood 4 to 8 times that necessary to inhibit the bacteria *in vitro*[37].

Streptomycin is active against bacteria which have proved most resistant to penicillin, namely the gram negative bacteria. It is also effective against some gram positive bacteria (Table III).

*Tularemia.* Strepomycin is the best therapeutic agent in this disease. An average amount of 1.0 Gm. daily should be given by intramuscular injection for five to seven days. In the severe typhoidal and pneumonic forms 2.0 Gms. should be given daily for seven days or longer until the disease is brought under control[37,58].

*Enteric Infections. Bacteremia*: Streptomycin has been used successfully to treat bacteremia in which *Esch. coli, Proteus ammoneai,* and *Ps. aeruginosa* have been isolated by bacteriological methods. Many of the gram-negative bacilli invade the blood stream

from the genito-urinary tract. If streptomycin is able to control the focus of infection and offspring of sensitive strains do not develop resistance successful treatment is assured. Unfortunately in some of these cases the infection is chronic and treatment is difficult. Daily doses of 2.0 Gm. for a period of 12 days have been given in some of these infections[37].

*Peritonitis.* Streptomycin is useful in the treatment of peritonitis resulting from leakage of gastrointestinal contents. Most cases, particularly peritonitis following appendicitis have received sulfonamides or penicillin, also, so that the usefulness of streptomycin alone is difficult to evaluate. Keefer *et al*[37] felt sufficiently encouraged from the accumulative experience in various clinics to recommend the use of streptomycin in all cases of peritonitis in which the offending organism is susceptible to its action. Streptomycin may be given intramuscularly 2.0 Gm. daily for five days or longer. Streptomycin can be injected directly into the peritoneal cavity.

*Urinary Tract Infections.* Streptomycin is a useful drug in the treatment of urinary tract infections[37,69] particularly when infection is of recent origin and the organism is a susceptible one. Results are not uniformly favorable. Complicated urinary tract infections of long duration in which the bacterial invaders are of mixed flora do not respond well to streptomycin. Finland and associates[59] have described the rapid development of resistance to streptomycin during treatment of urinary tract infections caused by various gram-negative bacilli. The appearance of resistant strains is a disturbing problem. The best results have been noted in infections due to *Proteus ammoneai* and *Ps. aeruginosa.* Strains of *Esch coli* may or may not respond well. The successful treatment of urinary tract infections may depend on administration of large doses from the beginning of treatment. The exact dosage is not known; 0.25 Gm. every six hours was not adequate in Finland's cases[59]. A large intake of fluid should be maintained and it is important that an effort be made to keep the urine alkaline[69]. In children receiving 0.02 Gms. per lb. body weight per day by intramuscular drip the concentration of streptomycin varied between 250 and 1000 units per cc. Most strains of gram-negative bacilli are responsive to this concentration of streptomycin.

*Hemophilus infections.* The two chief offenders in man are *H. influenzae,* and *H. pertussis.* Among the infections caused by the influenza bacillus are meningitis, laryngitis, otitis media, pericarditis, pneumonia and sepsis. Whooping cough is caused by *H. pertussis.*

*Hemophilus influenzae* infections are frequently severe. This organism causes meningitis in infants and young children. Prior to the use of sulfonamides almost all cases died. The sulfonamides helped, but the mortality rate was not strikingly reduced. In 1939 Alexander[60] prepared hyperimmune rabbits serum which is valuable in the treatment of this disease, particularly in older infants and young children. Streptomycin is now used in addition to these other forms of treatment. Despite these advances meningitis caused by *H.* influenzae, type b kills about 75 per cent of babies less than six months of age.

Alexander, Leidy, Rake and Donovick[61] treated 25 patients with streptomycin. The dose administered was 20,000 units (0.02 Gm.) per day given either by continuous intramuscular drip, in 240 cc. of isotonic saline, or by interrupted intramuscular injections in a concentration of 50,000 or less units per cc. The drug was administered intrathecally also. Injections were usually given once a day; the total intrathecal dose varied depending on the response of the patient (25,000-50,000 units).

Of the 25 patients 12 were considered mild cases. All recovered promptly using streptomycin; eight days was the average duration of treatment. Among nine severely ill cases five responded poorly and antiserum was necessary to bring about recovery. The remaining four responded poorly to sulfadiazine and serum; in these streptomycin was used with eventual recovery in three. In four very severe cases streptomycin, serum and sulfadiazine were used. All four recovered.

The following points are salient. Sensitive strains may develop resistance to streptomycin. Streptomycin is of value in the treatment of influenzal meningitis. Its beneficial effect seems to be augmentative to serum and sulfonamides. Streptomycin may be of value in the treatment of severe chronic cases which improve but are not cured by antiserum and sulfadiazine. Eighth nerve deafness may appear in patients treated longer than one week.

The treatment of pertussis occurring in man with streptomycin is promising; the disease course is shortened and less severe. The duration of the infective state is less prolonged as evidenced by the elimination of *H. pertussis* from the respiratory tract in the first week or so of the disease[64]. Bradford and Day[65] demonstrated the therapeutic effectiveness of streptomycin in murine pertussis prior to their use of this drug in human pertussis.

*Tuberculous Infections.* Although experimental studies[37,42] show that streptomycin inhibits the growth of tubercle bacilli, this antibiotic does not exert a rapidly curative effect in clinical tuberculosis. Streptomycin appears to have a place in the treatment of some forms of tuberculosis, but at this time it is not entirely clear just how effective

streptomycin is in all forms of tuberculous infection.

A number of patients with tuberculous meningitis have been treated with streptomycin. Some of these patients have apparently been cured, in others there is relief of symptoms. In this latter group tubercle bacilli can be found in the spinal fluid. Early diagnosis, confirmed by direct observation of tubercle bacilli and infection in guinea pigs, is desired for proper evaluation of results. Treatment may be instituted in rapidly progressive cases before the results of animal inoculation are at hand.

The treatment used by Hinshaw, et al[42], was 100-200 mg. of streptomycin intrathecally every 24 hours for two to six weeks and two to three Gm. intramuscularly daily for six months. A number of residual neurological disturbances have been noted among patients in whom the disease has been temporarily or permanently arrested. These are deafness, retrobulbar neuritis, ocular palsies, cerebellar dysfunction, and mental retardation.

It is hard to tell currently what the proper place of streptomycin is in the treatment of pulmonary tuberculosis. In general severe cases have been used for study. Since the natural course of pulmonary tuberculosis is erratic, the effect of treatment in these cases is difficult to define. It would appear in general that streptomycin has a beneficial effect on pulmonary tuberculosis. Further studies in progress in this country will settle the question within a short time.

Streptomycin has been used with good results in treating ulcerating tuberculous lesions of the respiratory tract. Tuberculous sinus tracts, usually secondary to tuberculosis lymphadenitis, have closed under treatment, but there has been recurrence when streptomycin was stopped. The treatment of tuberculous empyema has been disappointing. In renal tuberculosis palliative effects are noted. Arrest of renal tuberculosis has not been achieved with streptomycin.

Miliary tuberculosis, and other types of hematogenous tuberculosis respond favorably to streptomycin. In these cases, as those noted above, the dosage of streptomycin ranged from one to six Gm. daily, given intramuscularly. The minimum period of treatment, in respect to present knowledge, should be 90 to 180 days. Further data concerning streptomycin and tuberculosis will undoubtedly alter both dosage and duration of treatment.

## SUMMARY

This review brings together somewhat summarily recent clinical and experimental observations concerning two antibiotic substances, penicillin and streptomycin. Penicillin, used first in crude form, has been explored in the treatment of infections more completely than streptomycin. Its field of usefulness is wider than that of streptomycin. In the past few years with further purification of penicillin, a number of fractions have been identified, known in this country as penicillin F, G, K, and X. Commercial penicillins consist almost entirely of penicillin G; some may contain appreciable amounts of penicillin X. Some of these fractions are more active against bacteria than others[62,63]. Further clinical and experimental observations will be needed to fully evaluate the place of these penicillin fractions in therapy.

Streptomycin is a valuable antibiotic, but in comparison with penicillin, it has a number of drawbacks. It is more toxic to humans and bacteria quickly develop resistance to it. These limitations have been amplified in the text.

The search for antibiotics is carried on in many places. Undoubtedly, there will be additional substances found which will prove valuable in the treatment of diseases caused by microorganisms insensitive at this time to antibiotics which are not harmful to the economy of the human cell mass.

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# TYPHOID CARRIER STATE—TREATMENT BY CHOLECYSTECTOMY

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Wichita, Kansas*

Two of the earliest case reports of cholecystectomy for the typhoid carrier state are given in the A.M.A. Journal for April 26, 1913, by Thomas J. Leary, 1st Lt. M. C., U. S. Army, under the title, A Surgical Method of Clearing Up Chronic Typhoid Carriers. Both of his cases were in young men, soldiers who were under strict sanitary and medical control. The first was a man who had a chronic biliary fistula which alternately would close spontaneously, then have to be opened. After the fistula would close, the patient would have pain, fever, and a swelling of the gall bladder area. After being opened the symptoms would disappear and a clear mucoid material discharge for periods of days to weeks. After much treatment of various sorts, directed toward closing the fistula, had failed, a culture was made of the discharge which proved to be a pure growth of the typhoid bacillus. The stools were then cultured and found positive. The soldier had no history of clinical typhoid fever, but some years before had

*From the surgical service of Dr. James S. Hibbard, Sedgwick County Hospital.

been "unsuccessfully operated on for gall bladder stones" and later had a "drainage operation for empyema of the gall bladder." Surgical treatment was decided upon, and at operation he was found to have a stone impacted in the cystic duct, plus the external gall bladder fistula. The gall bladder and cystic duct were removed, the man made a good recovery and his stools became negative. Leary's second case was that of a soldier who had typhoid fever in the Philippine Islands in 1910, developed the carrier state and was treated many times in various ways, but persistently had positive stools. Finally in 1913 he was operated upon, at which time a distended gall bladder full of stones was removed. The contents of the gall bladder cultured out pure B. typhosus. This man also made a good recovery and his stools became negative.

The present case report is that of a white female in her middle thirties who was admitted to the Sedgwick County Hospital, Wichita, on January 17, 1947, with no complaints, but who stated that she was a typhoid carrier. Her initial trouble had started about a year ago with frank clinical typhoid fever. She was treated in a hospital for several weeks, became well, but her stools continued positive. She was finally dismissed under surveillance of the public health authorities, and recently moved to Wichita. Other past history was unilluminating. Physically she was healthy looking and not obese. There were no physical findings of interest. The urine was negative. The blood picture showed a variable white count of between ten and fifteen thousand at different times, and a sedimentation rate of 20 mm. in 60 minutes. The stool was positive for B. typhosus on several occasions. During her stay of almost a month before surgery she was treated variously with sulfasuxidine, methenamine, and penicillin, alone and in various combinations with no good result. X-ray examination on two separate occasions was reported as "non-visualizing gall bladder." Finally, on February 13, she came to operation. A right subcostal incision was used, as this approach has given better exposure in our experience and patients seem to have less postoperative pain with it. The gall bladder was small, thick-walled and contained a large number of small, many faceted stones. It was removed with ease, the stump of the cystic duct treated with phenol and alcohol and the wound closed without drainage. Silk was used throughout, with the exception of a single strand of fine catgut used to oversew the gall bladder bed. The anesthetic was ether, administered by the open drip method. A culture taken at operation from the gall bladder was positive for B. typhosus. The pathological report on the tissue was chronic ulcerative cholecystitis. The postoperative course was very benign, the highest postoperative temperature and pulse readings being 100.2 and 88 respectively. She was out of bed on the third day and the interrupted silk skin sutures removed on the eighth day without evidence of induration or inflammatory reaction around the sutures. Her stools remained positive for three weeks following surgery, and she was then given treatment with penicillin and sulfathiazole, following the recommendations of Comerford, Richmond and Kay, ("Typhoid Carriers Treated With Penicillin and Sulfathiazole",) in Lancet, 2:343, 1946. On March 13, and again on March 14, her stools were negative, and have remained so.

It is of course not possible to state unequivocally that her carrier state was relieved by surgery, for she was given other treatment following the operation, but it seems unlikely that medical treatment alone would have cured her, in view of the extensive pathology in the gall bladder, and experience has shown that surgery alone is effective in most similar cases.

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Treatment of urticaria and allied dermatoses should begin with small doses of benadryl, such as 50 mg. administered three times a day. The amount should be increased gradually until the minimal maintenance dose has been determined. Conversely, patients may require 300 to 400 mg. a day for several weeks, but frequently are able to decrease the amount gradually until smaller doses become equally effective.

Benadryl does not seem to exert cumulative action, for urticarial lesions promptly reappear when administration of the drug ceases. If relief is not obtained within the first few days, benadryl is unlikely subsequently to be of value, and administration of it should be discontinued. In our eleven months' experience with benadryl, no manifestation of cutaneous sensitivity has been observed, nor is there any evidence to date that benadryl is a habit-forming drug. Benadryl has a wide margin of safety and can be taken for many months in succession without deleterious results. It is just as effective in controlling urticaria in the fourth or fifth month of use as it is in the first.

Indiscriminate use of benadryl should be discouraged because severe side reactions sometimes occur, such as loss of judgment, confusion, or the sudden onset of drowsiness.—Proceedings of the Staff Meetings of the Mayo Clinic, August 7, 1946.

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Health, like freedom and wealth, cannot be given, but must be earned.—*Edward J. Stieglitz, M.D., A Future for Preventive Medicine.*

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Many a maternity patient has received obstetric care in its most literal sense—that is, care which is focused only on her reproductive organs—and died from tuberculosis or diabetes or cancer soon after delivery.—*Hazel Corbin, R.N., Journal of Nursing, August, 1946*

# CANCER OF THE CERVIX UTERI

Cancer of the cervix is far more frequent than is cancer of the fundus uteri. Yet cancer of the cervix accounts for four per cent of all cancer deaths while cancer of the body of the uterus accounts for six per cent of all cancer deaths. Earlier diagnosis in cancer of the cervix accounts for this discrepancy.

The first symptom of cancer of the cervix may not be a symptom but the discovery by the doctor at a routine pelvic examination of a suspicious area on the cervix. All women past the age of 35 should have pelvic examinations twice yearly. A speculum examination under a good light should be a part of this examination. If there are any suspicious areas on the cervix, biopsy should be done.

When infection, erosions, ulcerations, cystic change are found in the cervix, they should be treated as these lesions, in this location, may be precancerous. Postpartum and routine bi-yearly pelvic examinations have an important role in prophylaxis.

Abnormal bleeding and abnormal vaginal discharge are symptoms of cancer of the cervix. The bleeding is often postcoital or incidental to some other trauma and is often minimal in extent. Bleeding and abnormal discharge may be late symptoms. Urinary symptoms or frequency, burning or nocturia may be present.

Diagnostic measures include pelvic examination, including careful inspection of the cervix, and biopsy. If abnormal bleeding cannot be explained by the findings, diagnostic dilatation and curettage should be done to rule out a malignancy high in the cervical canal or in the fundus of the uterus.

Routine study of the vaginal secretion by the method of Papanicolaou may prove of great value in the early diagnosis of cancer of the cervix as well as corpus uteri.

The treatment of choice in cancer of the cervix is a combination of radium and x-ray therapy.

Prepared by Committee on Control of Cancer

# PRESIDENT'S PAGE

To the Members of the Kansas Medical Society:

While the general policies of the Kansas Medical Society are directed by the Council, composed of representatives elected by the delegates of each of the twelve councilor districts, the ideas back of these policies emanate from the twenty-six committees which are mandatorily appointed according to our constitution and by-laws.

In this issue of the Journal is a list of the personnel of these committees which have been selected after careful consideration. The duties of each committee are set forth in the constitution and by-laws. It is to be hoped that every chairman will realize the trust which has been placed in him to the end that he will call an early meeting of his committee and that each member will feel his obligation sufficiently to attend every meeting of his group.

There is an old adage which is apropos, "If two people exchange dollars, neither is richer; if two people exchange ideas, both are enriched." There is never a meeting of minds without this enrichment. Let us hope that the April 1948 issue of the Journal of the Kansas Medical Society will be filled with interesting activities of each and every committee.

The last twelve years have proved both the need and the value of improved social and political relationships between the Kansas doctors and the general public. We are awakening to our responsibilities as citizens, and while this does not diminish our duty in the continued advancement of scientific medicine, it indicates that we are also a social entity, both singly and collectively. It is certain that the time to continue to improve our relationships is now and always, thus making easier the work of our public policy committee.

L. S. Nelson

*President.*

# EDITORIALS

## Committees for 1947-1948

On the day following his installation as president, Dr. L. S. Nelson completed his committee appointments for the coming year. Weeks of planning preceded the final decision during which time Dr. Nelson consulted many Society members and in all instances the committee chairmen. Appointments have been made with several ideas in mind. Each doctor named on a committee was thought to have special information or special interest in that field. A second consideration was geographical distribution so that all sections of the state are represented on the various committees.

On Page VIII may be found the complete list of committee appointments for the coming year. Below are named the chairmen:

Allied Groups—O. W. Davidson, M.D., Kansas City.
Anesthesiology—P. H. Lorhan, M.D., Kansas City.
Auxiliary—C. O. West, M.D., Kansas City.
Child Welfare—B. I. Krehbiel, M.D., Topeka.
Conservation of Eyesight—W. M. Scales, M.D., Hutchinson.
Conservation of Hearing—J. N. Sherman, M.D., Chanute.
Constitution and Rules—A. W. Fegtly, M.D., Wichita.
Control of Cancer—H. E. Snyder, M.D., Winfield.
Control of Tuberculosis—G. B. Athy, M.D., Columbus.
Endowment—W. M. Mills, M.D., Topeka.
Executive—L. S. Nelson, M.D., Salina.
Expert Testimony—C. E. Joss, M.D., Topeka.
Hospital Survey—J. L. Grove, M.D., Newton.
Industrial Medicine—J. W. Spearing, M.D., Columbus.
Maternal Welfare—Porter Brown, M.D., Salina.
Medical Assistants—C. O. Merideth, Jr., M.D., Emporia.
Medical Economics—G. E. Kassebaum, M.D., El Dorado.
Medical Schools—Maurice Snyder, M.D., Salina.
Necrology—C. S. Huffman, M.D., Columbus.
Public Health and Education—D. D. Carr, M.D., Topeka.
Public Policy—J. L. Lattimore, M.D., Topeka.
Rural Health—C. M. Barnes, M.D., Seneca.
Stormont Medical Library—L. E. Eckles, M.D., Topeka.
Study of Heart Disease—P. W. Morgan, M.D., Emporia.
Venereal Disease—J. P. Berger, M.D., Wichita.
Veterans Administration Affairs—L. S. Nelson, M.D., Salina.

The Committee on Rural Health is listed for the first time. Appointed by Dr. Mills toward the close of his term of office, this committee remains as it was last year. It was originally appointed on the recommendation of the Council on Rural Health of the American Medical Association. From the A.M.A. came the request that each state society coordinate its rural health activities with those of the central organization. In Kansas, under the direction of Dr. C. M. Barnes, the committee will accomplish that and much more. A long, inspired agenda has been prepared, pointing toward activities that will be noticeable in every county of the state. The membership will hear more about this committee before the year is over.

Six committees have been eliminated this year. Dr. Nelson, in analyzing committee work, determined that certain committees could be combined to give all existing committees a larger sphere of activity. For instance, the Committee on Pharmacy has not been appointed, and this work will be directed by the Committee on Allied Groups. Dr. O. W. Davidson, chairman, has made elaborate plans and will shortly announce an outline of proposed activities, which will include cooperation not only with pharmacy but with all allied groups in the state.

The work on plasma will now be delegated to the Committee on Anesthesiology. This committee, under Dr. P. H. Lorhan, was organized last year and is now ready to expand its activities to where much more will be heard from them before the close of the fiscal year.

The Committee on Medical Schools has been enlarged to take in the responsibilities of the Committee on Postgraduate Study and the Committee on Scientific Work. Legal medicine will come under the Committee on Expert Testimony. Medical history is to be combined with the work of the Stormont Medical Library Committee.

Each of these committees has performed well and made many contributions to the Society. In the past, however, their work was limited to specific fields. Now, as a result of the combinations, each committee will have a larger responsibility and through the use of sub-committees will continue to carry on all activities that were separately listed in past years.

Dr. Nelson has high ambitions for committee accomplishments. He prepared a suggested agenda for each committee chairman and earnestly requests the active cooperation not only of each committee member but also of the entire Society. He will welcome, now or at any time, suggestions from the membership on ways in which committee activities

may be strengthened, and invites all members to consult with committee chairmen or with the Executive Office concerning problems in which they are interested.

## K. P. S. Claims Office

Kansas Physicians' Service, in existence less than a year and a half, already boasts an enrollment of 35,000 members or more. Almost every practicing physician in Kansas has signed a contract agreeing to participate in this public service project of the Medical Society. Hundreds of claims are processed each month, and in many areas where enrollment has been concentrated physicians are discovering that a sizable portion of their income is now being received from Kansas Physicians' Service. As this program grows, and enrollment is being accelerated at present, this situation will become true in many other communities of the state.

Beginning without experience and with a minimum of actuarial data, the officers and Executive Committee of Kansas Physicians' Service worked diligently to make this plan successful. They built a stable program and have already enlarged benefits in several categories without increasing the cost to the member. As experience justifies additional increases in benefits, these will be made. Financially the corporation is sound. The public has accepted the plan with enthusiasm, and the members of the Society have been most cooperative. The outstanding difficulty up to the present has been the delay in processing claims, and that problem has now been corrected to where almost every claim will be completed within a matter of days.

At the meeting of the Council of the Kansas Medical Society on May 16, it was recommended that a claims office be set up by Kansas Physicians' Service, separate and apart from the executive office of the Kansas Medical Society. This office will be directed by Mrs. Margaret R. Foster. Mrs. Foster is ideally qualified for this position. During her years with the executive office she became well acquainted with many members of the Society. For the past six months a large portion of her time has been occupied with matters pertaining to Kansas Physicians' Service. On May 29 she was employed by the Executive Committee of Kansas Physicians' Service to be in charge of the new office, as recommended by the Council, and as of June 1 will devote her entire time to the processing of claims and handling of correspondence between Kansas Physicians' Service and the doctors participating in the program.

Claims will be mailed to the Crawford Building as before, where financial and membership records will be checked. Claims then will be forwarded to the newly created claims office where Mrs. Foster will process them. All regular claims will be recommended for immediate payment. When further information is needed, letters will be written to the physicians. Payments that can not be allowed and all cases in which a question remains will be forwarded to the medical claims consultant for professional analysis and a decision. A relatively small number of claims, those in which matters of policy determine the decision, will be delayed and brought before the Executive Committee.

The Kansas Medical Society will continue to cooperate with Kansas Physicians' Service as before. The new claims office will work with the Medical Society but will be operated and paid for by Kansas Physicians' Service, relieving the Medical Society of an expense it formerly donated to the new corporation.

## E. M. I. C. Terminates

The Kansas State Board of Health announces the termination of the Emergency Maternal and Infant Care program, on June 30, 1947. After that date, no new maternity cases will be accepted. However, a child born under the program is eligible for services until he is one year old. Therefore, cases will be accepted for infants whose mothers were covered by the program at birth of the child, and will be authorized for care in cases of sickness, until the child is one year of age. For example, a child born in September of 1947 whose mother was an authorized case before termination of the program, June 30, 1947, will be taken care of at the existing rates until September of 1948.

The State Board of Health wishes to take this opportunity to thank the many practicing physicians who participated in the program, for without their participation the program would have been a failure. These physicians accepted cases as a part of their patriotic duty during a wartime emergency, when fees were high and there was a great personnel shortage. We know that many physicians refunded higher fees to accept fees at the E. M. I. C. rate when they realized that the patients were eligible for the program. Hospitals and physicians both exhibited unselfish attitudes in accepting and caring for these patients.

The Kansas State Board of Health has been interested in compiling some figures on the program. Many groups have asked for these figures and it is hoped that before long it may be possible to obtain them. The State Board of Health is interested in having comments from practicing physicians on the rules, regulations, pay rates, and administration of the program. Some physicians have felt that the program was responsible for the continued decrease in infant and maternal deaths,

while others have felt that it has had no effect. It is hoped by studying the statistics that we may be able to arrive at some conclusion.

As you know, the State Board of Health administered this program after it had been accepted by the Kansas Medical Society. Both the Medical Society and the Board of Health accepted the program as a patriotic duty. We both are happy to have participated in the program and hope we have been of some assistance during this great emergency.—*Division of Maternal and Child Health, Kansas State Board of Health.*

## Kansas Hospitals for the Insane

The Journal is always pleased when interest in articles printed is sufficient to prompt replies in the form of "Letters to the Editor." It is only from such sources that the Editorial Board learns the type of material that is most interesting to Journal readers.

In February a series of short articles on state institutions was begun, the first being on the three Kansas hospitals for the insane. At that time the Journal presented an outline of methods of holding sanity hearings, legal arrangements to be completed before patients may be admitted, and requirements for admission and discharge of patients. No mention was made of the facilities of the hospitals, personnel employed, or funds available.

After the article appeared in the Journal, the editor received a letter from Dr. Willliam C. Menninger, Topeka, who presented statistics on conditions existing in the Kansas hospitals for the insane. Since this information will be of interest to readers of the Journal, the letter is reproduced here.

"I read with special interest the little story about the State Hospitals in the February issue of the Journal. I think this is a fine idea. I wish, however, for the individual who wrote it, that he might have had an opportunity to see the Kansas Legislative council studies entitled 'Psychiatric Facilities in Kansas.' This was in two parts publications 143 and 145, dated November, 1946.

"These set forth in a vivid, plain and straightforward fashion the fact that we in Kansas in our mental hospitals are pretty nearly at the tail end of the state hospital systems in the country. They point out that our commitment laws are atrocious and recommend some radical revisions. They indicate that we have an annual per capita maintenance expenditure of $244 in contrast to a national average of $366. It indicates that we spend $105 of this amount on salaries and wages in contrast to a national average of $198. We rank forty-sixth out of the forty-eight states on this particular point. Where the national standards are set at one physician to 150 patients we run one physician to 372 patients at the Topeka State Hospital, one to 743 at Larned and one to 855 at Osawatomie. We have three graduate nurses for the entire state hospital organization. No outpatient clinics are maintained and no social workers employed.

"In brief, this blasts us pretty badly and I know that there is a group that John Lattimore has called together to try to figure out ways and means of getting support from us psychiatrists for some legislation. I just wonder whether the doctors of the state shouldn't know these facts."

## Osteopath Hospital Closed

Quintos W. Wilson, Wichita osteopath, was paroled for two years by District Judge J. N. Williams on a 60-day jail sentence, but his fine of $200 plus costs remained. The action was announced on May 16, and at the same time came news that the Southwestern Osteopathic Hospital in Wichita had been sold to H. N. Tihen, M.D., and other Wichita physicians.

Three years ago patients and employees at the Southwestern Osteopathic Hospital complained about surgery that was being performed by Wilson. When sufficient evidence had been obtained the county attorney took the matter before court and Wilson pleaded guilty to performing surgery without a license. The judge issued an injunction.

The State Board of Medical Registration and Examination worked closely with Wichita attorneys on the case and soon afterwards, discovering that Wilson continued his surgery, returned the matter to the courts. The district judge found that the defendant had violated his injunction and sentenced Wilson to 60 days in jail plus a fine of $200 and costs for contempt of court.

The case was taken to the Kansas Supreme Court where the decision was upheld. Subsequent activities remain somewhat obscure, but when the district judge prepared to invoke the sentence Carl I. Winsor, Wichita attorney assisting the prosecution, recommended a parole. The announcement was then made that the osteopathic hospital had been sold to a group of Wichita doctors of medicine, that the institution as such would be closed, that Wilson had been "helpful" in arranging the sale, and that he was leaving the state of Kansas.

The Kansas State Board of Medical Registration and Examination introduced a formal request that the court carry out the original sentence, but on the statement by the attorney employed locally for the prosecution, the jail term was withdrawn. However, the fine was ordered and the defendant placed on parole for two years.

## Dr. Olin West Resigns

Dr. Olin West, who was to have become president of the American Medical Association at its annual meeting in Atlantic City this month, has resigned because of ill health. Dr. Edward L. Bortz, Philadelphia, vice president, was inaugurated in his place.

Dr. Bortz was born in Greensburg, Pennsylvania, in 1896. He has been a fellow of the American College of Physicians since 1929, and he received the certificate of the American Board of Internal Medicine in 1937. In 1942 he was made a member of the Council on Scientific Assembly of the A.M.A., and in 1945 he became its chairman. He became a delegate to the A.M.A. the same year.

# 88th ANNUAL SESSION

## The Over-all Picture

Your editor has requested a report on the recent state meeting from an "outsider." Your ex-secretary is happy to report on a session as successful and as smoothly run as this meeting. To me it was the first truly post-war session with men in uniform conspicuously absent. Registered attendance was 1,142 including 555 physicians and 148 guests. In a busy year with hotel space at a premium, this was a creditable showing.

Monday, May 12, saw the usual gathering of golfers, trapshooters and hangers-on, climaxed by a banquet at the Topeka Country Club. These festivities add a day to an already crowded session, but the enthusiasm and large attendance are ample evidence that a day of relaxation without scientific programs is appreciated by a large part of the membership.

Meetings of the scientific session began Tuesday morning and were completed with only minor changes in the schedule by Thursday afternoon. These meetings, with the aid of the individualized round table lunches, offered a wide choice of opportunities in the theoretical and practical aspects of medicine in almost all fields. The Eye, Ear, Nose and Throat section ran concurrently in separate rooms throughout Tuesday and Wednesday with a good attendance at all meetings. Medical movies were shown almost continuously to good audiences from Tuesday morning to late Thursday afternoon. If there is any real criticism of the meeting it was the same as that of a three-ring circus, that there were too many things going on at once for any individual to take advantage of all that he would have liked.

The commercial exhibits with 60 booths arranged in a serpentine pathway leading to the scientific sections were crowded at nearly all times. One hundred twenty-six exhibitors were registered. There were, in addition, over 20 scientific exhibits prepared by individuals and organizations. These demonstrations of research offer a valuable field for further endeavor and may, in the future, warrant some type of subsidy. The Woman's Auxiliary of the Society met concurrently with the main session, and 170 members were registered. Preceding the session there was a successful meeting of the Kansas Medical Assistants' Society with 143 registered.

For entertainment, in addition to the program on Monday, there was the annual banquet at the local high school on Wednesday night, followed by an illustrated talk on the new Mexican volcano. There was no dance during this session. On Tuesday night two dinners were held, one for alumni of the University of Kansas and one for alumni of other schools. Both were well attended and excellent entertainment was furnished. After these meetings the Shawnee County Medical Society held open house in their rooms on West Eighth Street.

The first session of the House of Delegates was at 9:00 p.m. on Tuesday. Out of a possible total of 104 delegates, 62 were present. Thirty-nine component societies were not represented. At the second session, held at 4:00 p.m. on Thursday, 55 out of 104 delegates were present, leaving 43 societies unrepresented. It is hoped that certain constitutional changes regarding the time of these meetings which were adopted at this session can in some way help to correct this lack of interest. Reports of action taken in these meetings is reported elsewhere in the Journal. The plan of having all reports previously published and presented only in summary was again followed. This denies recognition to many hard-working councilors and committee chairmen, but saves time in an over-burdened meeting. Reports were presented for Kansas Physicians' Service and from the various state officers and delegates. A tribute was paid to those members and friends who were active in the recent legislative battle.

The thanks of the entire Society are due the Topeka membership for their hospitality and particularly to the chairmen of the committees whose hard work and thoughtful planning led to another successful meeting, culminating a year of progress for the Society. As long as Topeka and Wichita can stand the strain of sessions in alternate years, we are assured of excellent facilities for meetings, ample hotel space and committees who do far more than their share of the Society's work—*John M. Porter, M.D., Concordia.*

## President's Address

It is customary for your president at this time to present a paper or address dealing with a scientific subject, a philosophical aspect of medicine, economic changes which affect the profession, a summary of recent achievements or some historical data concerning our organization.

Before entering on any of the above mentioned efforts, I wish to express to you my appreciation and sincere thanks for the privilege of serving as your president during the past year. It is the highest honor this organization can bestow and the title of president is a source of pride and gratification to any recipient. I wish now to express my gratitude for the uniform courtesy and cooperation received from all members and our permanent staff, and beg that the same consideration be extended to my very capable successor, President-elect Dr. Laurence S. Nelson.

We have had numerous administrative problems, all of which have been adjusted satisfactorily. These, in part, have concerned the development of Kansas Physicians' Service and the Kansas plan for medical service to veterans which are administered by two competent executive committees. These both have necessitated many special as well as the regular meetings at frequent intervals. I beg to mention one or two points that appear to deserve special attention. Your Board of Directors of Kansas Physicians' Service has given many hours toward planning this voluntary, non-profit, prepaid medical care plan for Kansas. That they planned well is borne out by the more than 30,000 persons enrolled in this program during the first fifteen months of its existence, of whom one-half have joined since the first of this year. And the plan is financially sound for the entire debt to the Kansas Medical Society has been paid and Kansas Physicians' Service is solvent today. We urge your continued support of this project because it is your program, because the public wants it and because it is the only constructive answer so far devised that is effective against the planners who would see the medical profession dominated by politically appointed federal employees.

The other major continuing public service project of the society is our program for veterans care. We are well aware of the problems and annoyances that are involved, of the changing regulations, the detailed reports and of the seemingly endless confusion. Much of this was foreseen as inevitable before the agreement was signed. In such a

program regulations are necessary but the service you can render to the veteran is of such value that these details appear petty by comparison. Those of us who believe that the veteran should be permitted to select his physician will continue to cooperate and we sincerely hope that you will recognize the importance of this work and assist your society in this project. There is also hope that many difficulties with reference to this program have been solved. As the doctor becomes more familiar with the regulations of the Veterans Administration, and as the veteran learns to understand our agreement, much of the difficulty can be erased. The Veterans Administration, through its leaders in Washington, its officers in St. Louis and its personnel in this state, has made a sincere effort to cooperate with us. To insure the success of this venture, which incidentally has become a model for the nation, the Veterans Administration has set up an office in Topeka whose sole duty is to assist the designated doctors in their program. If every participating physician in Kansas will deal directly through the Medical Service Center at Topeka with reference to details regarding this program, many of the misunderstandings can be avoided. This office coordinates our agreement with the Veterans Administration and should be utilized by all of us in dealing with cases authorized for medical care as well as examinations for rating purposes.

This year has seen our society installed in adequate and beautiful quarters for its central office, and we urge everyone to see our permanent home, 512 in the New England Building at Fifth and Kansas Avenues, diagonally across the street from the post office. Our state committees have functioned in an especially efficient manner and will be thanked at another time.

We have continued to provide financial aid to our doctors returned from service who wish to take postgraduate courses of instruction and have fostered similar courses at the School of Medicine, as well as throughout the state. Our ex-service doctors are now taking a most active part in every phase of medical practice and it should be our constant desire to see them assume an increasing responsibility in directing the affairs of the Kansas Medical Society.

The months preceding the legislative session in part and the entire three months of the session were occupied with the recurring biennial encounter to preserve high standards of medical practice in Kansas. The outcome was the most devastating defeat ever suffered by the opposition and, we believe, established the principle that a license issued by the Kansas State Board of Medical Registration and Examination will become prerequisite to the practice of medicine and surgery in Kansas. The return of medical officers from service reduced the previous critical areas in Kansas until now there remains no extended area nor any community of considerable population without resident medical care. This fact effectively rebutted the war time argument of lesser trained persons that their services were needed.

A second factor influencing the legislature at this session was the excellent quality of medical care being rendered by the members of our society. Community pride in the local doctor of medicine was frequently expressed by members of the legislature.

But beyond that, a large number of doctors took time to personally inform their representatives and senators of this problem. You doctors advised with the legislators regarding the importance of training, the value of standards and what this meant to the lives and health of the people. This, perhaps more than any one thing, influenced the result because your legislator usually knew how he would vote even before coming to Topeka. I wish to pay especial tribute to you members who assisted in this effort and will always recall with pride the uniform support you gave those of us who were charged more directly with the immediate responsibility at Topeka. The credit for this result belongs to the entire society as well as to a special planning committee. Of course, special commendation goes to our executive secretary and to a former president, now treasurer of this society, who happens to be a state representative from this community.

It has been a long time since any mention has been made of the meetings in the early days of the Kansas Medical Society so I would like to review briefly the early days of our society. The Kansas Medical Society was founded in 1859, eighty-eight years ago. In that same year John Brown left Kansas for the East and on October 17 raided the arsenal at Harper's Ferry, thereby providing the curtain raiser for the Civil War. It was not until 1861 that Kansas was given statehood and it was still the bloody battleground of pro and anti slavery forces in 1859.

The Kansas Medical Society was chartered by an act of the Territorial Legislature meeting at Lawrence on February 10, 1859.

The first section of the act provides that "Amory Hunting, S. B. Prentiss, J. P. Root and their associates and successors who shall be elected to membership as hereinafter provided, are hereby constituted a body corporate and politic by the name of the Kansas Medical Society, and shall have perpetual succession forever." The Supreme Court of Kansas in 1881 said that the territorial charter had not been nullified by admission to statehood, that the act only limited the life of the corporation to the end of all human affairs and the close of finite existence and that the medical society was endowed with perpetual succession or immortality. Hence a later law limiting the life of a corporation did not apply to our society.

We are the oldest corporation in Kansas and the only one with a perpetual charter which never has to be renewed.

Among the incorporators of our organization we find the name of Charles Robinson who later became governor of the state, the only physician to attain that honor.

The charter, among other more customary provisions, allows the society to make and enforce by-laws, also to impose and collect by lawful process fines up to $50 for violation of the by-laws.

Section 6 says: Said society shall issue certificates of membership to its members, and may also grant licenses to all respectable physicians, non-graduates, who shall on examination be found qualified for the practice of medicine and surgery or either, to practice those branches for which they are qualified.

The act is signed by A. Larzalere, Speaker of House of Representatives, C. W. Blalock, president of the Council, S. Medary, Governor of the Territory of Kansas.

The first meeting of our society with twenty-nine physicians present was held the same day the legislature passed the act, organization was effected and officers elected including Dr. S. B. Prentiss as president. A second meeting was held at the Eldridge House in Lawrence February 23, 1860, and a third, a year later, in the same place. Due to various catastrophic episodes including Quantrill's raid and the Civil War, there were no meetings until 1866 and it is interesting to note that in the minutes of this meeting a committee was appointed to confer with the Regents of the State University in regard to the establishment of a medical department thereto. It is probably correct that

the society entered on a continuous existence at this meeting and our meetings at one time were numbered consecutively from this date. It is interesting to find that the address of President C. A. Logan in 1866 is largely directed against patent medicines. He says, "True it is that false professors like false prophets require but a definite time to exhibit their unworthiness and work out their ruin, but the principle of quackery is a very phoenix, no sooner dying in one form than it is ready to rise again and take wing over more extensive plains and feast upon the fruitfulness of more productive fields." Our presidential addresses today are not quite so "literary."

Dr. O. D. Walker of Salina, while president over thirty years ago, recorded his recollection of these early officers and founders of the Kansas Medical Society. Dr. D. W. Stormont was the recording corresponding secretary of that term, as well as many to follow.

Quoting from Dr. Albert Newman's presidential address to our society in 1868, Transaction KMS, Vol I, pp. 99-100:

"Not long since in one of the daily papers of Lawrence (Lawrence Republican, T. Dwight Thacher, editor) appears the following modest local:

'A Surgical Triumph. We were shown yesterday an example of what is now called "conservative" surgery. One of the engineers employed by the Union Pacific Railway Company had his left hand severely crushed in coupling cars last October. Many surgeons would have unhesitatingly amputated it at the wrist. Dr. Wilder, of this city, however, took charge of the case, exsected the crushed bones of the hand, and succeeded in saving the third and fourth fingers in good condition, so that the man can still manage his engine and have considerable use of his hand.'

"I called upon the editor and directed his attention to what I considered an unjust and uncalled for aspersion upon the medical profession. I endeavored to show him that he was not sufficiently conversant with the principles of medicine to speak with any such positiveness as to what 'many surgeons' would do under any circumstances, and that particularly in this case, as he did not see it after the injury and before the operation, but only after several months had elapsed, it was impossible for him to know that 'many surgeons' would not have saved three fingers instead of two. In the course of our conversation, the editor stated that the reason for his using the language to which I objected, was that the doctor used a similar but stronger expression in explaining the case to him; that the doctor's language was 'that nearly every surgeon would have unhesitatingly amputated at the wrist.' A statement which certainly showed a very modest appreciation of his own skill, if not a very thorough knowledge of the general practice of surgeons. After a full discussion of the subject, the editor refused to admit that his language was in any respect unjust, and asserted in the most positive manner that he believed the statement was entirely true. I candidly confessed to him my great surprise at finding him so utterly incapable of appreciating the true relation which, as a journalist, he bore to the medical profession."

So we see that there were difficulties even in those far off days with some of the brother physicians who sought publicity in the press and with the editors who encouraged it.

Dr. W. L. Schenck, still living ex-president of 1878, said on an occasion similar to this that we need more state medicine and continues, "The state of Kansas has passed but one law for the prevention of disease and that was in the interest of her horned population." And he quotes a letter from Doctor Sinks at Leavenworth which says, "There is no board of health in this city . . . The hogs run at large in our streets and are the only scavengers . . . There is a health committee of the city council with the powers conferred upon cities of the first class. When a contagion prevails to an alarming extent, they do what the public demands. In other words, after the horse is stolen they lock the door."

This condition seems a far cry from modern sanitary science and health laws, yet it is in the professional life of one man.

Their only revolutionary medical discovery was anesthesia in that far off medical time—pre-Pasteur, pre-Lister, pre-Roentgen, pre-miracle drugs. How many of us could have done so well with tools so poor?

We can well take pride in the founders of our state society and be grateful for our rich heritage.

These pioneers of medicine in Kansas were interested in medical ethics, in their own professional improvement, in medical organization, in medical education, public health and medical investigation. Their aims and ideals should not be lost or regarded lightly, for they lighted a torch which has never gone out.—*W. M. Mills, M.D.*

## Report of Journal Editor

The present Editorial Board of the Journal of the Kansas Medical Society took over with the issue for May 1946, and the members have been striving monthly to make the Journal a better scientific publication.

The Board has met one noon each month to discuss current problems and outline the policies of the Journal. Original articles are distributed for editing, often by two or more members of the Board, and final decision for acceptance or rejection of articles of questionable value has been put to a vote of the Board as a whole.

First class scientific articles continue to be the major problem of the Editorial Board. For one issue we were so low on scientific articles that we had to beat the bushes for articles and practically had no choice except to accept and publish those articles that we could get. It is sincerely hoped that during the next year worthwhile articles will become so plentiful that we can increase the number of scientific pages in the Journal.

During the past year the Editorial Board saw the need for and sanctioned the publication of a roster of the members of the Kansas Medical Society, which was mailed to you in August 1946. We have received many favorable comments on this issue. It is not the intent of the Board, however, to make this a yearly event. The roster was published as a starting point for the Kansas Medical Society to continue or delete as they see fit.

In March 1947, the first annual University of Kansas School of Medicine number of the Journal of the Kansas Medical Society appeared. It is the desire of the present Editorial Board that this University of Kansas School of Medicine number be continued through the years to come as a tribute to the members of the medical staff who, in the past, have contributed so many worth while articles for publication.

The Editorial Board is desirous of receiving comments concerning the Journal, critical or otherwise, and will welcome any suggestions which will make it a better publication.

The Editorial Board is most grateful to Miss Pauline Farrell, our managing editor, for her fine work, many suggestions and faithful cooperation. We are deeply indebted

to Oliver Ebel, our executive secretary and business manager of the Journal, for his many editorials and counsel. We are also indebted to the many physicians of Kansas and the guest speakers of past medical meetings for their contribution of scientific articles for publication.

And last, but not least, we are indebted to those firms who have seen fit to purchase advertising space in the Journal. We sincerely hope that those advertisements have paid dividends, for without this source of income the Journal could not exist without financial aid from the Society.—*Lucien R. Pyle, M.D.*

## First Session, House of Delegates
## May 13, 1947

The meeting opened with the call to order by the president, Dr. W. M. Mills.

Reading of the minutes was waived by unanimous consent and the minutes printed in the Journal of the Kansas Medical Society were accepted as printed.

Dr. A. W. Fegtly announced a quorum present.

Mr. Blake Williamson was introduced and gave a brief account of the activities of the last legislature. He stated that one of the biggest needs in Kansas today, in his opinion, is to interest doctors in going into the smaller communities. Hospitals which are equipped to train interns should be allowed to do so. He paid a fine tribute to Dr. J. L. Lattimore for the splendid work he did in the legislature. The victory won in this year's legislature, he said, is due in a very large part to his efforts and those of many physicians in their own communities. In discussing the State Board of Medical Registration he mentioned the debt that Kansas medicine owes to Dr. J. F. Hassig and commented on his sacrifices to uphold the standards of medical practice in this state.

A standing vote of thanks was offered to Mr. Williamson for the many things he has done for Kansas medicine.

Dr. John M. Porter briefed the councilor reports and Dr. Milton B. Miller reported on committee activities.

Suggested amendments to the by-laws were read by Dr. A. W. Fegtly, these having previously been printed in the Journal. These were tabled until the second meeting. It was moved and duly seconded to re-print the by-laws since many amendments have been added. Motion carried.

In the absence of Dr. Conrad M. Barnes, the chairman of the newly created Committee on Rural Health, Dr. L. E. Beal read a report submitted by that committee. This was referred to the second meeting of the House of Delegates.

Dr. W. M. Mills reported briefly on the activity of the Committee on Veterans' Affairs.

Dr. Barrett A. Nelson reported on the activities of Kansas Physicians' Service. At the annual meeting of the Board of Directors, Dr. Dwight Lawson was elected secretary-treasurer, the office formerly held by Dr. W. M. Mills. The affairs of the national organization, Associated Medical Care Plans, Inc., were described.

In the absence of Dr. L. R. Pyle, editor, Dr. Dwight Lawson read the report of the Editorial Board of the Journal of the Kansas Medical Society.

The report of the executive secretary was read by Mr. Oliver E. Ebel.

Dr. W. M. Mills extended an invitation received from Miss Louise McNeal to visit the new Stormont Medical Library in the State House.

The report of the constitutional secretary was presented by Dr. John M. Porter, showing present membership to be 1,509 paid, service and honorary members.

Because the auditors' report had not been completed, Dr. J. L. Lattimore, treasurer, asked to be allowed to present his report at the second meeting.

Resolutions were read by Dr. John M. Porter as follows:

The Oklahoma State Medical Society recommends the discontinuance of hospital staff meetings during the summer months. Oklahoma delegates will introduce this resolution at the House of Delegates of the American Medical Association, and their society requests Kansas to support the action. This resolution was tabled until the second meeting.

The Colorado State Medical Society presented two resolutions, one regarding the proposed change of policy of American specialty boards, the other referring to clarification of rules relating to medical service fees received from the federal government. These resolutions were tabled until the second meeting.

Brief reports on the winter meeting of the American Medical Association were given by Dr. J. F. Hassig and Dr. F. L. Loveland.

Brief messages were given by the president and president-elect.

It was announced that councilors from districts 4, 5, 9 and 11 must be elected, and members from those districts were asked to prepare elections to present to the second meeting.

Dr. Henry N. Tihen, as chairman of the Public Policy Committee, commented on the fine work done by Clarence G. Munns in the matter of public relations.

The following resolution was presented by Dr. Henry N. Tihen:

"WHEREAS: The Kansas Medical Society through its component county societies, has raised a sum of money by volunteer subscription, allocated for the specific purpose of aiding Kansas returned service physicians of World War II in defraying expenses of refresher or postgraduate courses, and

"WHEREAS: Certain physician service men belonging to this Kansas Medical Society have lost their lives while in service,

"BE IT RESOLVED: That the House of Delegates hereby authorize and instruct the committee in charge of this fund to make available to the widows of these deceased service physicians, upon petition or otherwise, a sum equivalent to the proportionate amount which would have been available to these physicians for refresher or postgraduate work."

This resolution was referred to the second meeting of the House of Delegates. There being no further business, the meeting adjourned.

## Second Session, House of Delegates
## May 15, 1947

The meeting was called to order by the president. After Dr. A. W. Fegtly reported a quorum present, the meeting proceeded.

Under unfinished business, the amendments suggested by the Committee on Constitution and Rules were presented for vote.

The amendment to the By-Laws, Chapter X, Editorial Board, Section 7, changing the manner of disbursing Journal funds and the signing of checks, was approved.

Amendment to By-Laws, Chapter V, House of Delegates, Section 1, declaring that two meetings must be held on

separate days rather than requiring that they be on the first and last days as at present, was approved.

Amendment to By-Laws, Chapter V, House of Delegates, Section 17, limiting the term of office of AMA delegates to six years, was not approved.

The resolutions which had been read at the first meeting were briefed and voted upon. The resolution offered by the Oklahoma Medical Society regarding hospital staff meetings during summer months was rejected. The resolution presented by the Colorado State Medical Society concerning a change in policy of American specialty boards was approved. The second resolution presented by Colorado concerning a clarification of rules relating to medical service fees received from the federal government was rejected.

The resolution presented at the first meeting regarding authorization of funds to be given to the widows of Kansas service physicians was approved.

The treasurer's report was read by Dr. J. L. Lattimore, and a vote of thanks was extended to him for his fine service.

Regarding the committee reports read at the first meeting, it was moved and duly seconded that these reports be scrutinized and acted upon by the Council. Motion carried.

The next order of business was election of officers.

Dr. O. W. Davidson was nominated as president-elect. It was moved, duly seconded and carried that the nominations be closed and the secretary be instructed to cast a unanimous ballot.

Dr. J. H. A. Peck was nominated as first vice president; it was moved, duly seconded and carried that the nominations be closed and the secretary be instructed to cast a unanimous ballot.

Dr. F. R. Croson was nominated as second vice president; it was moved, duly seconded and carried that the nominations be closed and the secretary be instructed to cast a unanimous ballot.

Dr. Dale D. Vermillion was nominated as constitutional secretary; it was moved, duly seconded and carried that the nominations be closed and the secretary be instructed to cast a unanimous ballot.

Dr. J. L. Lattimore nominated Dr. Henry S. Blake for treasurer and Dr. L. F. Barney nominated Dr. J. L. Lattimore for treasurer. The tellers announced Doctor Lattimore elected and it was moved, duly seconded and carried to make the vote unanimous.

Dr. F. L. Loveland nominated Dr. John M. Porter as delegate to the American Medical Association for a term of two years. It was moved, duly seconded and carried that the nominations be closed and the secretary be instructed to cast a unanimous ballot.

The next order of business being the election of councilors, the representatives from the councilor districts involved were asked to report their elections. There was considerable discussion of the proper interpretation of the length of time which can be served by a councilor elected to fill an unexpired term. It was ruled that the intent of the Constitution was that no councilor should serve more than six years. Therefore, if councilors are re-elected after having served part of an unexpired term in addition to a full term, they must be prepared to resign after serving six years. Upon this premise, the president asked for announcement of election of councilors. The following were named:

District 4—Dr. Frank Foncannon to serve two more years.

District 5—Dr. L. J. Beyer to serve a three-year term.

District 9—Dr. Dale Vermillion to serve a three-year term.

District 11—Dr. J. R. Campbell to serve two more years.

The first meeting of the Council was announced to take place immediately after the close of this meeting.

Dr. L. S. Nelson was then installed as president for the coming year and paid a fine tribute to Dr. W. M. Mills for his splendid service during the past year.

A vote of thanks was offered to the Shawnee County Medical Society for a fine meeting.

There being no further business, the meeting was adjourned.

## Eye, Ear, Nose and Throat Society

At a meeting of the Kansas Eye, Ear, Nose and Throat Society held during the annual meeting of the Kansas Medical Society, Dr. Clifford J. Mullen, Kansas City, was named president for the coming year and Dr. Byron J. Ashley, Topeka, was elected secretary.

## Psychiatric Society

The Kansas Psychiatric Society announces the following officers for the coming year: president, Dr. Lewis L. Robbins, Topeka; vice president, Dr. J. F. Casey, Topeka; secretary-treasurer, Dr. Edward D. Greenwood, Topeka; counsellors, Dr. E. M. Wiedenmann, Topeka, and Dr. Paul E. Davis, Parsons.

## Obstetrical and Gynecological Society

Dr. Howard C. Clark, Wichita, will serve as president of the Kansas Obstetrical and Gynecological Society this year and Dr. Clyde O. Meredith, Jr., Emporia, will be secretary of the organization.

## Kansas Heart Association

The Kansas Heart Association, composed of a group of members of the Kansas Medical Society, was officially organized at a meeting held on Wednesday, May 14. By-laws were drawn up and officers were elected.

Dr. Philip W. Morgan, Emporia, was named president. Other officers are Dr. Fred J. McEwen, Wichita, vice president; Dr. Don C. Wakeman, Topeka, secretary-treasurer; Dr. Eugene D. Liddy, Lawrence, delegate to the American Heart Association.

For some time it has been felt that the overall plans of the American Heart Association could best be carried out through a local organization, and several years ago a group of Kansas physicians who had taken a course arranged by the Society's Committee on the Study of Heart Disease called themselves the Kansas Heart Association. No formal organization was maintained, however, and those present at the meeting last month agreed that they could best extend the objectives of the committee to all physicians in the state interested in heart disease through an established society. Plans for the coming year will be outlined after the meeting of the American Medical Association and the American Heart Association.

## Golfing and Trapshooting Tournaments

Sportsman members of the Kansas Medical Society enjoyed their annual golf tournament and trapshoot in Topeka on Monday, May 12. At a short business session, the following officers were elected: president, Dr. H. P. Jones, Lawrence; vice president, Dr. R. R. Sheldon, Salina; secretary, Dr. J. W. Shaw, Wichita; directors, Dr. W. K. Hobart, Topeka; Dr. J. L. Wentworth, Arkansas

City, and Dr. L. L. Cooper, Fort Scott; chairman of trapshoot, Dr. W. A. Smiley, Jr., Junction City.

Winners in the golf tournament at Topeka Country Club were: first low gross, Dr. Glen Ashley, Chanute, 77; second low gross, Dr. Ed Ashley, Chanute, 78; third low gross, Dr. R. R. Sheldon, Salina, 80; first low net, Dr. A. P. Cloyes, El Dorado, 59; second low net, Dr. H. L. Barry, Wichita, 61; third low net, Dr. C. C. Parmley, Wichita, 64. In the nine hole flight Dr. Les Saylor and Dr. B. I. Krehbiel, both of Topeka, tied for low gross with scores of 47, and Dr. Paul Powell, Topeka, had low net, 33.

Dr. W. G. Brown, Paola, won first in the trapshoot with a 91, followed by Dr. W. A. Smiley, Sr., Junction City, and Dr. G. L. Gill, Sterling, with scores of 88.

Prizes for the sports events were donated by the following firms: Capitol Sporting Goods Company, Farnsworth Laboratory, Goetze-Niemer Company, Schering Corporation, American Optical Company, Pitman-Moore, Sharp and Dohme, Eli Lilly and Company, Ciba Pharmaceutical Products, Philip Morris and Company, Munns Medical Supply Company, Commercial Casualty Insurance Company, Quinton-Duffens Optical Company, Mead Johnson and Company, William F. Merrell Company, Gerber Baby Foods Company, Siebrandt Manufacturing Company, Davis and Geck, Riggs Optical Company, and W. E. Isle Company.

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Cancer ranked second as a cause of death in 1945 when sex and age were not considered, according to a chart released by the Division of Public Health Statistics in Kansas Cancer Notes for March, 1947. Among females, cancer ranked first as a cause of death in all age groups between the ages of 30 and 64.

## Officers and Councilors

Printed below is a list of the officers and councilors of the Kansas Medical Society who will comprise the governing body of the Society during the next fiscal year.

President, Laurence S. Nelson, M.D., Salina

President-elect, O. W. Davidson, M.D., Kansas City

Past President, W. M. Mills, M.D., Topeka

First Vice President, J. H. A. Peck, M.D., St. Francis

Second Vice President, F. R. Croson, M. D., Clay Center

Secretary, D. D. Vermillion, M.D., Goodland

Treasurer, J. L. Lattimore, M.D., Topeka

AMA Delegate 1945-1947, F. L. Loveland, M.D., Topeka

AMA Delegate 1947-1949, Philip W. Morgan, M.D., Emporia

AMA Delegate 1948-1950, John M. Porter, M.D., Concordia

COUNCIL

First District, R. T. Nichols, M.D., Hiawatha
Second District, L. G. Allen, M.D., Kansas City
Third District, C. H. Benage, M. D., Pittsburg
Fourth District, Frank Foncannon, M.D., Emporia
Fifth District, L. J. Beyer, M. D., Lyons
Sixth District, Warren F. Bernstorf, M.D., Winfield
Seventh District, R. R. Cave, M.D., Manhattan
Eighth District, Ben H. Mayer, M.D., Ellsworth
Ninth District, D. D. Vermillion, M.D., Goodland
Tenth District, Murray C. Eddy, M. D., Hays
Eleventh District, John R. Campbell, M.D., Pratt
Twelfth District, G. R. Hastings, M.D., Garden City


## Schedule of Refresher Courses

## Offered By

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in cooperation with
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KANSAS STATE BOARD OF HEALTH

**September 9-11, 1947.....Anesthesiology**
**October 20-23, 1947.....Tuberculosis**
**November 17-20, 1947.....Obstetrics and Gynecology**
**December 8-10, 1947.....Physical Medicine**
**January 19-21, 1948.....Radiology and Cancer**
**February 16-19, 1948.....Internal Medicine, Psychiatry and Dermatology**
**March 15-17, 1948.....Surgery**
**April 12-15, 1948.....Pediatrics and Public Health**
**May 3-7, 1948.....Ophthalmology and Otolaryngology**
**May 25-27, 1948.....Nursing Education and Hospital Administration**

**The program of postgraduate courses for the year starting July 1, 1947, also includes a Continuation Course on SURGICAL PATHOLOGY, meeting for the full day on Thursdays, for a term of twelve weeks starting on September 25. Continuation Courses in other subjects will be announced for later dates; also a Circuit Course on PSYCHOSOMATIC MEDICINE will be offered in five different centers of the state in November—definite dates to be announced soon.**

## Editorial Board

The affairs of the Journal of the Kansas Medical Society will be administered during the coming year by seven physicians, five from Topeka who will serve as members of the Editorial Board, and two from other parts of the state who will be associate editors. The complete list is as follows:

Lucien R. Pyle, M.D., Editor, Topeka
John W. Cavanaugh, M.D., Topeka
Orville R. Clark, M.D., Topeka
Dwight Lawson, M.D., Topeka
Don C. Wakeman, M. D., Topeka
C. A. Hellwig, M.D., Wichita
James B. Weaver, M.D., Kansas City

## Kansas Physician's Service

Officers and directors of Kansas Physicians' Service for the 1947-1948 year are as follows:

President, Barrett A. Nelson, M.D., Manhattan
Vice President, John L. Lattimore, M.D., Topeka
Secretary-treasurer, Dwight Lawson, M.D., Topeka
Executive vice president, Oliver E. Ebel, Topeka

DIRECTORS

Conrad M. Barnes, M.D., Seneca
C. H. Benage, M.D., Pittsburg
W. F. Bernstorf, M.D., Winfield
R. R. Cave, M.D., Manhattan
Athol Cochran, M.D., Pratt
O. W. Davidson, M.D., Kansas City
Frank Foncannon, M.D., Emporia
J. L. Grove, M.D., Newton
G. R. Hastings, M.D., Garden City
O. A. Hennerich, M.D., Hays
Holmes Meade, Topeka
W. M. Mills, M.D., Topeka
L. S. Nelson, M.D., Salina
E. M. Sutton, M.D., Salina
M. F. Trued, Topeka
D. D. Vermillion, M.D., Goodland

## Orthopedists Announce Change

A change in general qualifications for eligibility to the examination of the American Board of Orthopedic Surgery has been announced by the secretary of the board, Dr. Francis M. McKeever, Los Angeles.

After January 1, 1951, all candidates applying for Part 1 of the examination must have the following general qualifications: (1) he must be a citizen of the United States or Canada; (2) he must be a graduate of a medical school approved by the Council on Medical Education and Hospitals of the American Medical Association; (3) he must have served an internship of 12 months in a general hospital acceptable to the board; (4) he must have spent a year on an approved surgical residency subsequent to the completion of his internship. No individual may apply for Part I of the examination if he has not completed at least one year in special orthopedic training in addition to meeting the general requirements.

The board has provided an exemption under the second classification above for those whose training has been received outside the United States or Canada. Such an applicant must present satisfactory credentials to the Council on Medical Education and Hospitals and to the National Board of Medical Examiners, and must have been engaged in the practice of orthopedic surgery in the United States and Canada for at least three years prior to submission of his application.

Complete information on Part I and Part II of the examination may be secured from the secretary of the board, 1136 West 6th Street, Los Angeles 14, California.

## Indiana Requires Registration

The state of Indiana recently passed a law requiring annual registration of physicians, to become effective July 1, 1947. The licenses of those who do not comply with the law will be revoked, so the Indiana State Board of Medical Registration and Examination is taking this means of advising physicians who hold licenses in Indiana that they must register. Complete information may be secured from the Indiana board, 416 K. of P. Building, Indianapolis 4, Indiana.

# COUNTY SOCIETIES

The Reno County Medical Society held a dinner meeting on May 7 with Dr. Robert H. Riedel, of the Kansas State Board of Health, as speaker. Dr. Riedel discussed cancer registry and cancer clinics in Kansas. New officers of the Reno County Society are as follows: president, Dr. Irl E. Hempstid; vice president, Dr. E. L. Fitzgerald; secretary-treasurer, Dr. John Jarrott.

* * *

A group of 40 doctors from northeast Kansas held a meeting at the Sabetha country club on April 24. Dr. Paul Shafer, assistant professor of surgery at the University of Kansas School of Medicine, spoke on "Newer Concepts of Peptic Ulcers," and Dr. John L. Lattimore, Topeka, discussed medical economics.

* * *

Members of the Marshall County Society and members of the Auxiliary in that county held a joint dinner meeting in Waterville on May 8. A business session in the office of Dr. D. M. Diefendorf folowed the dinner.

* * *

Dr. Hobart Allebach of Kansas City, formerly of Ottawa, was guest speaker at a meeting of the Franklin County Society held at Ottawa April 30.

* * *

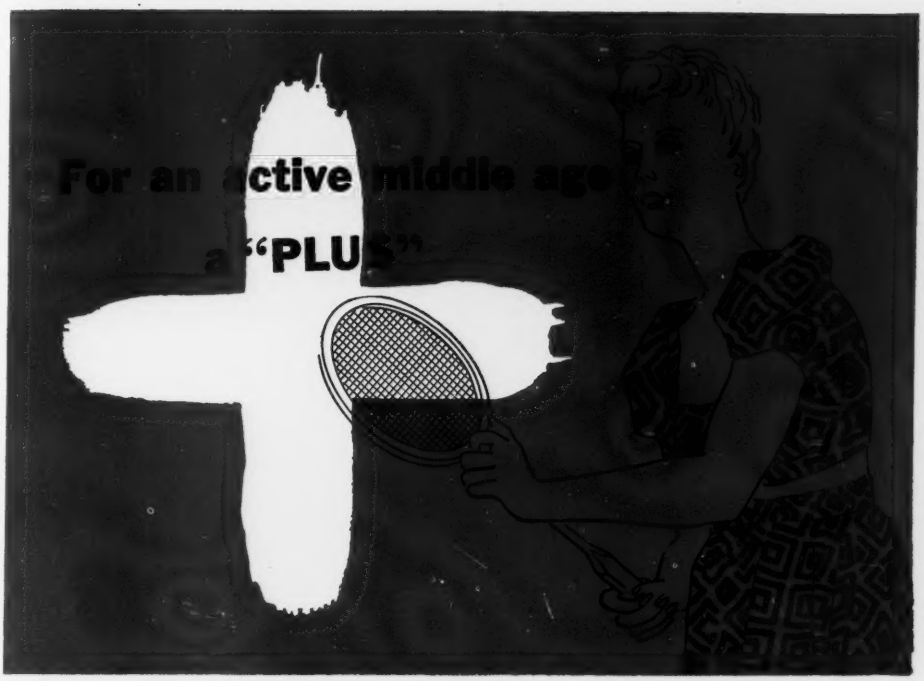
A joint meeting of the Stafford County Medical Society and Auxiliary was held at the home of Dr. and Mrs. W. L. Butler, Stafford, May 19. A covered dish dinner was served, after which there was a social hour.

* * *

A meeting of the Anderson County Society was held May 16 at Manners' Inn, Garnett. The construction of a county hospital received approval of the group, and suggestions were made for the operation of a hospital if a proposed bond issue is passed.

* * *

The April meeting of the Crawford County Society was held on the 24th at Pittsburg. Dr. C. W. Erickson told of the postgraduate course he recently completed at the University of Michigan, and Dr. C. B. Newman, Dr. E. J. Schulte and Dr. Paul B. Leffler discussed malaria conditions observed overseas while in military service.

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Tablets of 1.25 mg.....bottles of 20, 100 and 1000.
Tablets of 0.625 mg.....bottles of 100 and 1000.
Liquid, containing 0.625 mg. in each 4 cc. (1 teaspoonful).....bottles of 120 cc.

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# MEMBERS

Dr. H. L. Graber, assistant superintendent of the Sedgwick County Hospital, Wichita, for the past year, has begun practice in Nickerson.

* * *

Dr. L. L. Saylor, who has been a resident in surgery at Hines General Hospital, Chicago, for the past year, has returned to practice in Topeka.

* * *

Dr. Ralph I. Canuteson, Lawrence, attended the third national conference on health in colleges in New York early this month, and served as chairman of the planning committee for the conference.

* * *

Dr. J. H. A. Peck, St. Francis, attended a meeting of the American College of Surgeons in Winnipeg, Canada, last month and appeared on the program.

* * *

Dr. A. K. Owen, Topeka, was recently elected to emeritus fellowship in the American College of Radiology.

* * *

Dr. Balthasar A. Brundardt, Salina, has announced that his son, Dr. Bernard A. Brungardt, is now associated with him in practice. The younger Dr. Brungardt was graduated from the Creighton School of Medicine and completed his internship at St. Catherine's Hospital in Omaha.

* * *

Dr. M. W. Wells, who has been practicing in LeRoy, is closing his office there and has not announced plans for the future.

* * *

Dr. John D. Green, McPherson, announces that he is now associated in practice with Dr. Robert P. Watterson, a graduate of the Iowa University Medical School. Dr. Watterson was recently released from the Navy after having served since 1942, 20 months in the Pacific as a flight surgeon.

* * *

Dr. C. J. Bliss, Perry, has been named Jefferson county health officer.

* * *

Dr. J. N. Carter, who has been practicing in Garnett, is moving to Ottawa. He will retain his office in Garnett, however, and will be assisted in practice there by Dr. David Laury, a graduate of Northwestern University School of Medicine.

* * *

Dr. G. W. Wright, who has been practicing in Webb City, Missouri, during the past year, has returned to Neodesha and is resuming his practice there.

* * *

Dr. G. B. Sekavec, who has been practicing in LaCrosse, has moved to Oakley and has opened an office there.

* * *

Dr. Lennel Wright, Wichita, has opened an office in Haysville, 10 miles south of Wichita, and will practice there one or two days each week.

* * *

Dr. J. C. Ulrey, St. John, has been reappointed Stafford county health officer.

Dr. Leon Zimmerman, who is on terminal leave from the Army, is taking a postgraduate course in eye work in Portland, Maine, before returning to his practice in Liberal.

* * *

Dr. William C. Menninger, Topeka, was named president of the American Psychiatric Association at a meeting held in New York last month. He will take office in 1948.

## DEATH NOTICES

### JOHN DRYER GREEN, M.D.

Dr. John D. Green, 44, died May 11 in McPherson. A graduate of the University of Nebraska College of Medicine in 1931, he practiced first in China, spending six years in that country. He returned to the United States in 1938 and spent the next two years in postgraduate work in surgery, opening an office in McPherson in 1940. He was a member of the McPherson County Medical Society.

* * *

### OTTO B. KIEHL, M.D.

Dr. Otto B. Kiehl, 67, who had practiced in Pittsburg for 40 years, specializing in pediatrics, died at his home there May 10. He was graduated from the University of Kansas School of Medicine in 1907 and took postgraduate work at Harvard and at schools in Germany and Austria. He was a member of the Crawford County Medical Society and had served as president of that group.

* * *

### LEROY S. S. OTT, M.D.

Dr. Leroy S. S. Ott, 59, an honorary member of the Finney County Medical Society, died at his home near Longdale, Oklahoma, May 4. After his graduation from the Kansas Medical College, Topeka, in 1910, he spent two years as surgeon for a mining company in Colombia, South America, and then returned to Kansas. He had practiced here since that time, in Mayetta, Tribune, Fort Dodge and Leoti, until his retirement two years ago. During World War I he served in the Army Medical Corps.

* * *

### SANFORD BAILEY, M.D.

Dr. Sanford Bailey, 75, a member of the Finney County Medical Society, died April 28 at Garden City. He had been practicing since 1893, and had been in Kansas since 1910. He was graduated from the Kentucky School of Medicine, Louisville, in 1893 and practiced in Kentucky for seven years before opening an office in Lakin. In 1914 he moved to Garden City, continuing practice there until his death, except during World War I when he served in the Army Medical Corps.

* * *

### MAYER SHOYER, M.D.

Dr. Mayer Shoyer, 71, a member of the Jackson County Society, died April 5 at his home in Holton. He had practiced there for many years and at the time of his death was serving as county physician. A graduate of the University Medical College of Kansas City in 1897, Dr. Shoyer practiced in Soldier before moving to Holton.

*Announcing:---*

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**CHARLES HUGGINS, M.D.**, of the University of Chicago;

**JOE VINCENT MEIGS, M.D.**, of Vincent Memorial Hospital, Boston;

**HUGH J. MORGAN, M.D.**, of Vanderbilt University, Nashville.

**A. W. OUGHTERSON, M.D.**, New York, Medical Director, American Cancer Society;

**HARRY C. SOLOMON, M.D.**, of Harvard University, Boston;

**EUGENE F. TRAUB, M.D.**, of Columbia University, New York;

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## Premarital Health Examinations In Kansas*

On and after July 1, 1947, every person marrying in Kansas must obtain a medical examination, including a standard blood test for syphilis, from a physician. The examination and blood test must be made within 30 days before a marriage license is issued. The law which was finally passed by the legislature differs in a number of respects from the original bill introduced. More than 32 states have passed similar laws and in many others such legislation is now pending. While laws of this type have as their primary objective the finding of syphilis, physicians should not overlook the excellent opportunities in the field of preventive medicine.

In 1946 approximately 70,000 marriages were performed in Kansas, of which 55 per cent were marriages of out-of-state applicants. Under the premarital law and the law requiring a three-day waiting period, both of which were recently passed by the legislature, requirements for marriage applicants of Kansas will now be somewhat similar to those of surrounding states. This, undoubtedly, will result in our total marriages dropping to a more normal level of 35,000 annually. We could reasonably expect then a minimum of 70,000 persons, to a large extent young adults contemplating marriage, to contact their physicians for an examination each year.

This contact is of utmost importance to the applicant, the physician, and to the state of Kansas. To the applicant, it provides an opportunity for a complete health inventory, together with sound medical advice at one of the crucial periods of his life. To the physician, it brings to his office a young adult about to make one of the most important decisions of his life. The contemplated marital relationship will directly influence the health and lives of others. The physician has a grave responsibility and, on the other hand, one of the finest opportunities to focus the attention of this potential family member on the benefits to himself and family members secured through continuous use of modern medical services and facilities. The physician, through his understanding, diplomacy, and professional skill, at this particular time can instill confidence, trust, and respect which may result in medical services being extended at the most opportune times for complete protection of the individuals of this potential family. The state has everything to gain in a situation which gives promise of reduction of both morbidity and mortality in this young group of home builders in whose hands rests the future of the state.

*The procedure for examination in Kansas under the premarital law is as follows*:

1. The applicants for a marriage license consult a physician for an examination and blood test.

2. The physician sends a specimen of blood to an approved laboratory. This specimen must be designated as a premarital test.

3. The laboratory examines the specimen of blood, fills out the upper half of the certificate form; then it completes the laboratory report of serological test for syphilis in triplicate, giving the original copy to the physician, sends a duplicate to the Kansas State Board of Health at Topeka, and retains the third copy in its files.

4. After careful examination of the applicant and the laboratory report, the physician completes the certificate and gives it to the applicant.

5. The applicant signs the certificate at the bottom of the form and presents the completed certificate to the probate judge who issues a marriage license, after the three-day waiting period has elapsed.

The approved laboratories will be supplied with the certificate forms, entitled "Marriage Health Certificate." The physician will receive one certificate form from the laboratory for each applicant for whom he submits a specimen of blood designated as "premarital." The laboratory statement does not give the result of the test, which will be sent to the physician on a separate report, to be retained by him.

The decision as to whether or not the marriage license is issued rests with the probate judge. The physician is required only to examine and certify his opinion as to: (1) whether or not the applicant is infected with syphilis; (2) shows symptoms indicating infection with other venereal disease; (3) if so infected, whether or not the disease is in a communicable or potentially communicable stage, and (4) whether or not the applicant is feeble minded.

If the physician feels that the individual has an infection which is transmissible to his marital partner, he undoubtedly will not sign the certificate, but will make every effort to place the applicant under treatment. When the physician later feels that the patient is free of infection, a new application form can be completed.

The law forbids the issuance of a marriage license by a probate judge if the physician certifies that an applicant is infected with syphilis; therefore, the physician must exercise his judgment as to the interpretation of "infection with syphilis." Those persons who have had treatment for syphilis adequate to insure their non-infectivity, who have sero-resistant (Wassermann-fast) infections, or who may not have syphilis despite a positive blood serological test, may be declared to be "not infected with syphilis" in the opinion of the physician. The refusal of a license by the probate judge may be appealed to the judge of the district court, who may order its issuance.

It is expected that the usual fee for medical examination be paid by the applicant; however, the law provides that "any county or city health officer shall, upon request of any applicant, perform the examination and make the certificate required hereunder, without charge." The law further provides that laboratory tests may be made on request without charge at the laboratory of the State Board of Health at Topeka.

*Procedure for examination outside of Kansas*:

1. Certificate forms can be obtained from the Kansas State Board of Health, Topeka.

2. Certificate forms of similar content, nature, and character provided by other states having comparable laws shall be acceptable for non-residents of Kansas.

3. Serological tests for syphilis must be performed within 20 days prior to issuance of a marriage license.

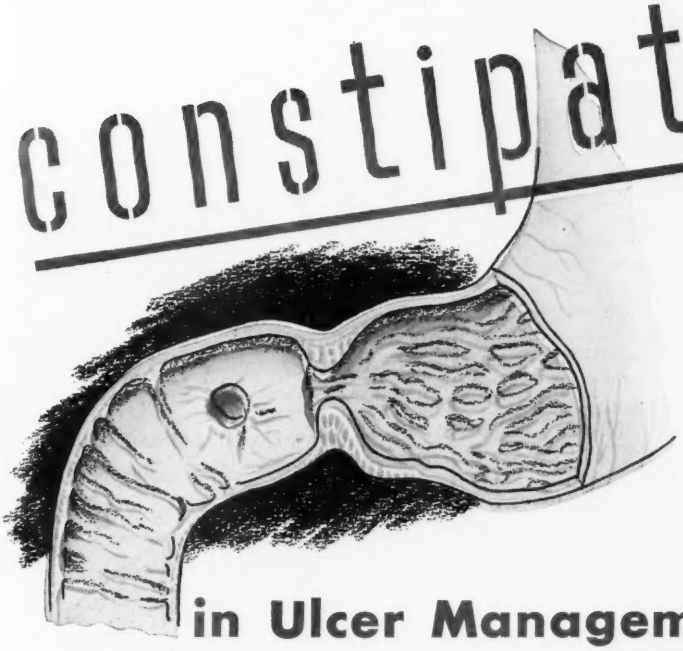
4. Any state laboratory, U. S. Public Health Service laboratory, U. S. Army or Navy laboratory, or any laboratory aproved by the State Board of Health of the state in which said laboratory is operated, shall be considered approved.

5. Forms issued by the Army and Navy will be accepted for military personnel.

The law provides a penalty for misrepresentation of the facts called for by the certificate form, or for failure to comply with the provisions of the act. Any person violating the provisions of the act shall be guilty of a

*This timely explanation of premarital health examinations is presented in the June issue of the Journal in the space ordinarily devoted to one of the state institutions. The series of articles on state institutions will be continued in July.

# constipation



## in Ulcer Management . . .

**"Constipation is not an important symptom of ulcer, but is often the outstanding complaint. Many patients either disregard the 'indigestion,' distress or pain . . . Such patients frequently become established cathartic addicts, with resultant bowel dysfunction and abdominal discomfort to confuse the distress picture."**

—Portis, S. A.: Diseases of the Digestive System, ed. 2, Philadelphia, Lea & Febiger, 1944, p. 199.

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misdemeanor, and, upon conviction, shall be fined not less than one hundred dollars nor more than five hundred dollars.

The law further provides a similar penalty for violation of the confidential nature of all certificates, laboratory statements, reports, files and records, other than the marriage license or the application therefor. These shall not be divulged or open to inspection of any person other than state or local health officers or their duly authorized representatives, except by written permission of the party or parties concerned.

The premarital law is distinct from the three-day waiting period law, which provides that three days must elapse between the filing of an application for and the issuance of the marriage license.

The laboratories which have been approved by the State Board of Health for performing serological tests for syphilis, up to the present, are as follows: (Other laboratories will be approved as they qualify for approval.)

1. Division of Public Health Laboratories
   Kansas State Board of Health, Topeka
2. Lattimore Laboratories, Topeka
3. Dupray Laboratories, Hutchinson
4. University of Kansas Hospitals, Kansas City
5. Sackett Laboratory, Kansas City
6. Wichita City Health Department, Wichita
7. Bethany Hospital, Kansas City
8. Wichita Clinical Laboratory, Wichita
9. St. Francis Hospital, Wichita

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**FOR SALE**—Vertical fluoroscope, shockproof, excellent condition. Write the Journal 10-47.

## Medical Reserve Organization

Plans are being made for the organization of various medical units in Kansas as part of the overall organized reserve program, according to information received from Col. C. C. Higgins, Topeka, who is in charge of the program in this area. Officers in the grade of major and captain are particularly desirable at this time, and those not now in the O.R.C. are asked to apply for commissions.

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# Life expectancy 30 days?

Infant mortality during the first 30 days of life is on the *increase*. While the total infant mortality has been declining, the proportion of those who died within the first month *has actually increased* from 52.7% to 62.1%*. During this fatal first month the infant should be given every possible benefit. One step in the right direction is good feeding. In this way the gastro-intestinal hazards of excessive fermentation, upset digestion and diarrhea may be minimized.

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Simply prepared in hot or cold milk, 'Dexin' brand High Dextrin Carbohydrate provides well-taken and well-retained nourishment. 'Dexin' *does* make a difference.

*Vital Statistics—Special Reports: Vol. 25, No. 12, National Office of Vital Statistics, Washington, D. C. (Oct. 15) 1946, p. 206.

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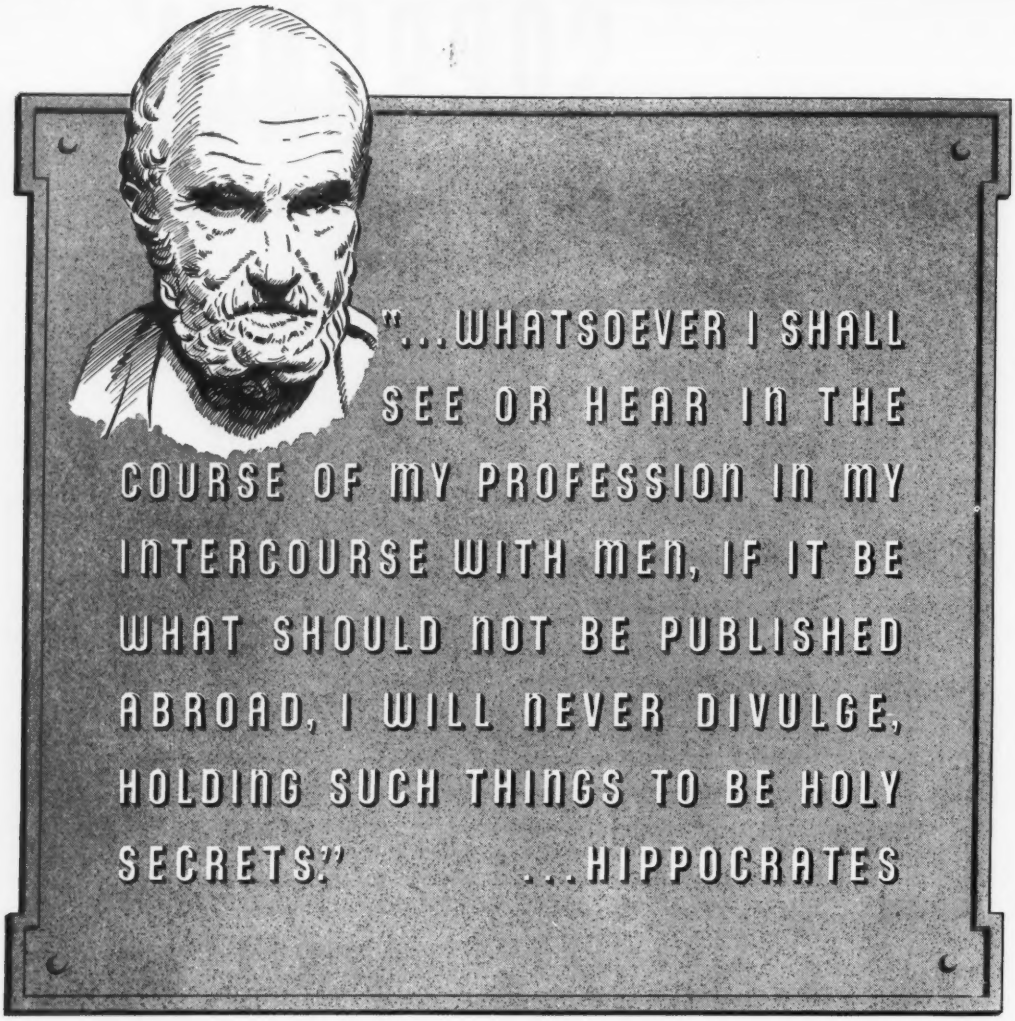
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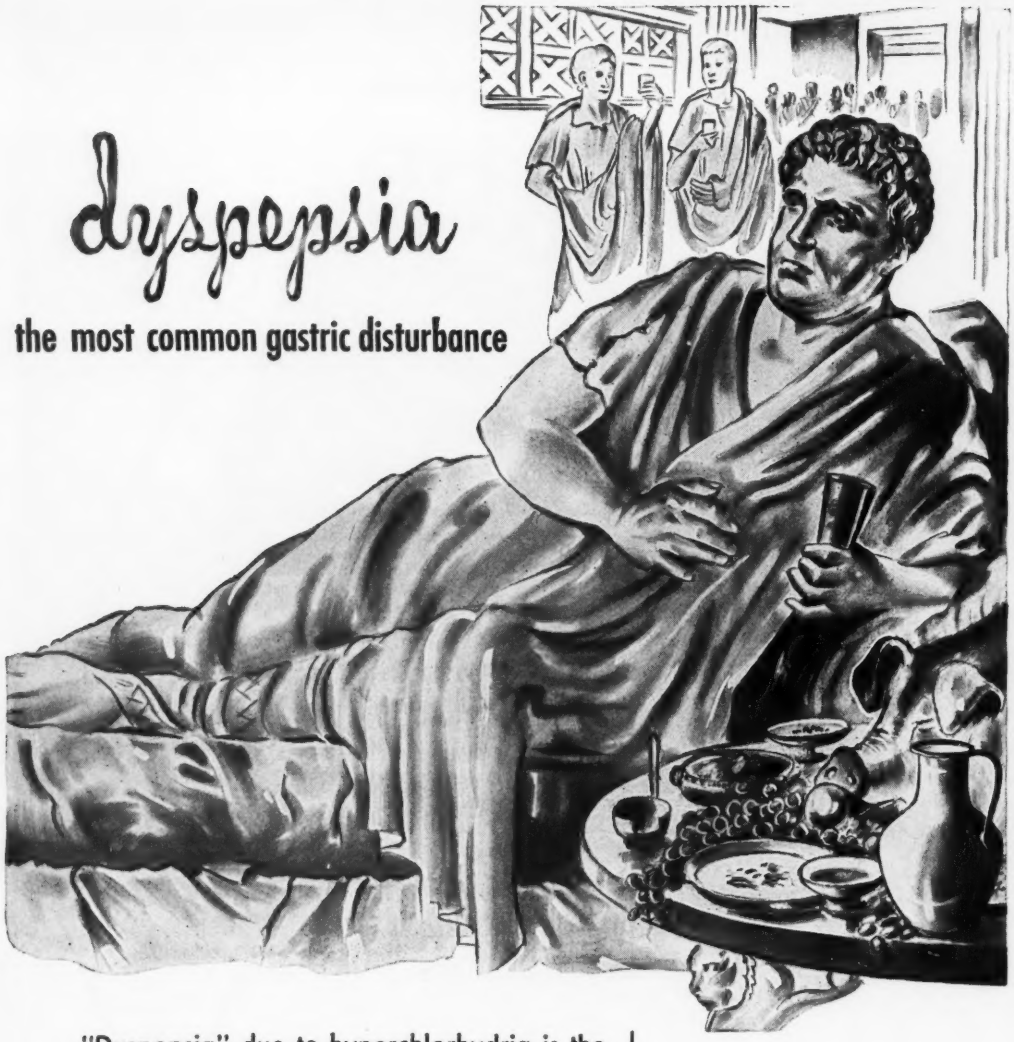

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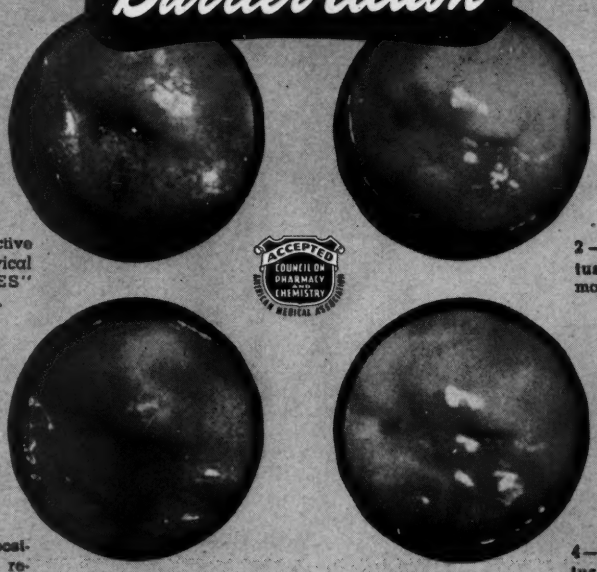

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DURING recent years there has been a sharp increase in the incidence of ulcer of the stomach. Some doctors report that within eight years ulcer cases have increased by as much as 100%.

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SEE YOUR DOCTOR! If you have frequent stomach pains or "indigestion," don't dose yourself. You may get temporary relief from your symptoms, but the medication you use may actually make your ailment worse. See your doctor and let him decide the cause of your trouble. He alone is qualified to diagnose your case and recommend treatment. Ask his help at the first sign of something wrong.

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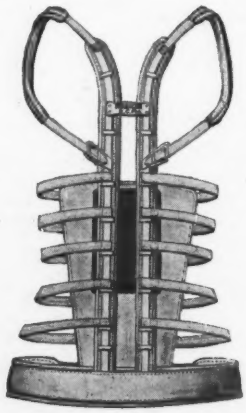

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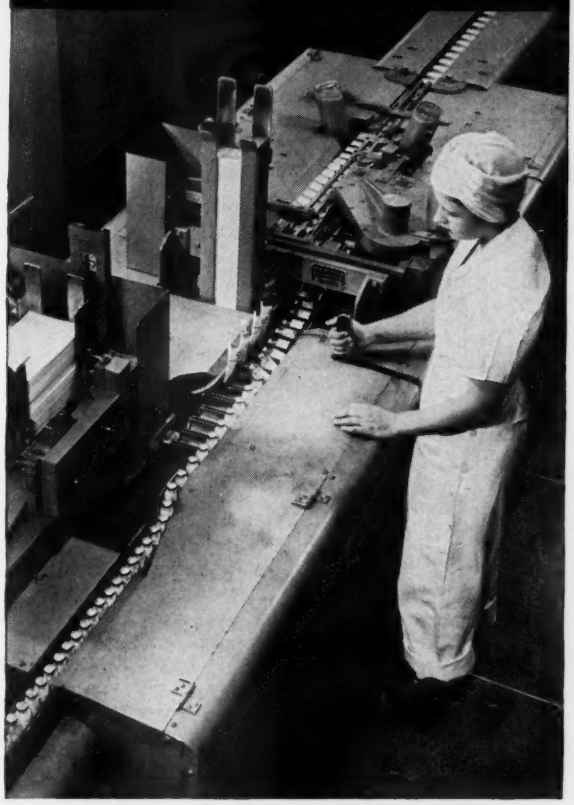

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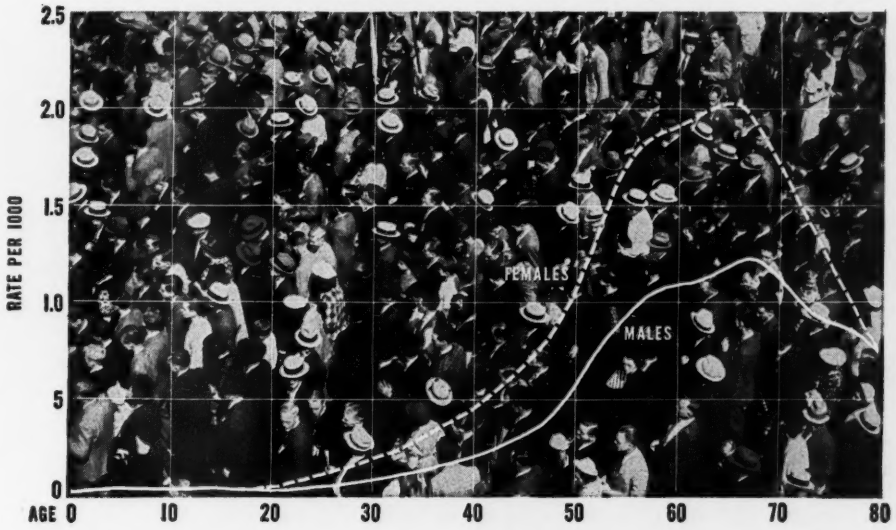


Of our present population, about 4,000,000 will become diabetic sometime in their lives. More than 4% of females and 2% of males under 50 will acquire the disease. With an increase of 50,000 a year, their number will grow in the next few decades at a rate greater than that of the total population. When our population reaches its expected maximum in 1985, it will be 22% larger than in 1940—but by then the diabetic population may increase by 74%[1,2]

Control with but *one injection a day* of 'Wellcome' Globin Insulin with Zinc has been made possible for many diabetic patients who formerly required *multiple injections* of regular insulin alone or in conjunction with protamine zinc insulin. Favorable results with Globin Insulin have been achieved by virtue of the following advantages:

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*'Wellcome' Globin Insulin with Zinc is available in 40 and 80 units per cc., in vials of 10 cc. Accepted by the Council on Pharmacy and Chemistry, American Medical Association. Developed in The Wellcome Research Laboratories, Tuckahoe, New York. U.S. Patent No. 2,161,198.*

1. Spiegelman, M., and Marks, H. H.: Am. J. Pub. Health 36:26 (Jan.) 1946. 2. Statistical Bull., Met. Life Ins. Co. 27:6 (Feb.) 1946.

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1. Surg., Gynec. and Obst 74:390 (Feb. 16) 1942.

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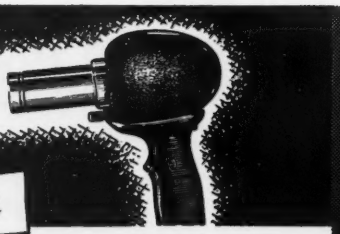

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***Provides Adjustable Spot of Light***

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for oral and [illegible] feeding

Like Amigen, Protolysate i[illegible] digest of casein and consi[illegible] acids and polypeptides. Like Amigen, Protolysate supplies the nitrogen essential for maintenance, repair and growth.

Unlike Amigen, which may be employed both orally and parenterally, Protolysate is designed only for oral use.

1 LB. NET (454 GM.)
MEADS
PROTOLYSATE
For Oral Administration
A dry enzymic digest of casein containing amino acids and polypeptides, useful as a source of readily absorbed food nitrogen when given orally or by tube. Protolysate is designed for administration in cases requiring predigested protein. The mode of administration and the amount to be given should be prescribed by the physician.
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.

1 lb. cans at drug stores

MEAD JOHNSON & CO., EVANSVILLE 21, INDIANA

There is no shortage now of AMIGEN for parenteral use. There is no shortage now of PROTOLYSATE for oral use.